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

Addendum to Project A23-42 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ATC classification	Anatomic Therapeutic Chemical classification
COVID-19	Coronavirus Disease 2019
COVRIIN	Expert Group on Intensive Care, Infectious Diseases and Emergency Medicine
CRF	Case Report Form
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PrEP	pre-exposure prophylaxis
RCT	randomized controlled trial
RKI	Robert Koch Institute
RKI	Robert Koch Institute
RT-PCR	reverse transcriptase-polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SOC	System Organ Class
SPC	Summary of Product Characteristics
WHO	World Health Organization

1 Background

On 26 September 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-42 (tixagevimab/cilgavimab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the data of the PROVENT study presented in the dossier of the pharmaceutical company (hereinafter referred to as the "company") [2], taking into account the information from the commenting procedure [3].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

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

For this research question, the company presented analyses of a subpopulation of the PROVENT study in its dossier [2]. The PROVENT study is a double-blind randomized controlled trial (RCT) comparing COVID-19 PrEP with tixagevimab/cilgavimab versus placebo in adults unvaccinated at baseline who are at increased risk of inadequate vaccine response or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. For a detailed study description, see the dossier assessment [1]. 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 statutory health insurance (SHI) system.

According to § 2 of the COVID-19 Prevention Ordinance, persons who are immunodeficient or at increased risk of an inadequate COVID-19 vaccine 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 provision of prescription drugs for pre-exposure prophylaxis [4].

The PROVENT study was not included in the assessment. In the dossier of the company, sufficient information was only available for a part of the subpopulation formed by the company, so that for the majority of the subpopulation it was impossible to determine to what extent the criteria of the Prevention Ordinance are fulfilled [1].

In the commenting procedure, the company subsequently submitted information on the characteristics of the study participants in the presented subpopulation [3].

PROVENT study unsuitable for the benefit assessment

The information on the characteristics of the study participants for the PROVENT study [3] subsequently submitted by the company in the context of the commenting procedure is also insufficient to justify the suitability of this study for the benefit assessment. This is explained below.

As described in dossier assessment A23-42 [1], the company operationalized the presented subpopulation of the PROVENT study based on the following 4 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, human immunodeficiency virus (HIV), treatment with corticosteroids or other immunosuppressive drugs) and an increased risk of inadequate vaccine response
4) Contraindication to SARS-CoV-2 vaccines in the presence of at least one risk factor for a severe course of COVID-19

In its comments, the company explains how many study participants were included in the presented subpopulation on the basis of each of these 4 criteria, with some of the study participants exhibiting several of the criteria at the same time. This is described below.

Criterion 1: immunosuppressive disease at baseline

For criterion 1, the company states that this was operationalized via the System Organ Class (SOC) "immune system disorders" according to the Medical Dictionary for Regulatory Activities (MedDRA), whereby study participants whose immune system disorder was recorded solely on the basis of the high-level group term "allergic diseases" were excluded from this, as according to the company, a relevant impairment of the immune system cannot be assumed due to an allergic disease alone. Based on this criterion, a total of 25 study participants were included in the subpopulation presented by the company, of which 6 were included exclusively using this criterion.

For this criterion, the company still has not provided any information on the specific underlying diseases and the respective disease severity. It thus remains unclear whether all study participants included in the subpopulation via this criterion meet the criteria of the Robert Koch Institute (RKI) for a risk of reduced vaccine response [5] mentioned in the dossier assessment.

Criterion 2: treatment with immunosuppressants at baseline

For criterion 2, the company states that study participants were included in the presented subpopulation if a preparation belonging to the therapeutic subgroups "antineoplastic agents" (ATC2 = L01) or "immunosuppressants" (ATC2 = L04) of the Anatomic Therapeutic Chemical (ATC) classification was documented as concomitant medication at baseline. Based on this criterion, a total of 163 study participants were included in the subpopulation presented by the company, of which 9 were included exclusively using this criterion.

However, the company still has not provided any information on the immunosuppressive drugs used or their dosages or on the underlying diseases. As already described in the dossier assessment, according to the RKI, underlying immunosuppressive disorders or therapies do

not per se lead to a relevant limitation of the immune response. The degree of immunodeficiency is rather dependent on the severity of the disease or the dosage of the immunosuppressive drugs used [5].

Criterion 3: Impaired immune system (due to organ or bone marrow transplantation, primary immunodeficiency, HIV, treatment with corticosteroids or other immunosuppressive drugs) with concomitant increased risk of inadequate vaccine response

In its comments, the company explains that study participants were only included in the submitted subpopulation via criterion 3 if the presence of an "impairment of the immune system due to solid organ transplantation, blood or bone marrow transplantation, immunodeficiency, HIV infection, use of corticosteroids or other immunosuppressive drugs" was documented by the investigator in the Case Report Form (CRF) by means of a corresponding specific question. Based on this criterion, a total of 495 study participants were included in the subpopulation presented by the company, of which 324 were included exclusively using this criterion.

The data subsequently submitted by the company show that 225 study participants (43% of the subpopulation presented) had HIV infection. It is unclear for how many study participants this was the only reason for inclusion in the subpopulation via criterion 3. As described by the RKI [5], a relevant impairment of the immune system is not to be assumed across the board in the presence of an HIV infection, but this concerns HIV patients with ≤ 200 CD4+ cells and/or detectable viral load. Information on how many patients this applied to is not available for the PROVENT study.

Criterion 3 is also defined by treatment with corticosteroids or other immunosuppressive agents. Corticosteroids do not fall under ATC codes L01 or L04, through which criterion 2 is defined. It is therefore possible that study participants were included in the subpopulation solely through the administration of corticosteroids. No information is available on how many study participants were concerned here. According to the study report, 396 study participants in the total PROVENT study population received systemic corticosteroids. In the appendix to its comments, the company submitted a list of the immunosuppressants used in the context of concomitant medication, which, however, does not include any information on the number of study participants affected or the form or dosage used. The information in the company's comments is therefore not suitable to clarify the existing ambiguity regarding this criterion.

Criterion 4: Contraindication to SARS-CoV-2 vaccines in the presence of at least one risk factor for a severe course of COVID-19

Regarding criterion 4, the company states that study participants were included in the presented subpopulation on the basis of this criterion, for whom both the item "intolerance

to vaccine" was determined in the CRF by an investigator and for whom, moreover, there was at least one risk factor for a severe course of COVID-19. Based on this criterion, a total of 10 study participants were included in the subpopulation presented by the company, of which 9 were included exclusively using this criterion.

Overall, the operationalization of this criterion is comprehensible. However, only few study participants were included in the presented subpopulation due to criterion 4.

Information on existing underlying diseases

In addition to the information on the 4 criteria described above, the company provides information on existing underlying diseases in its comments, divided into the following disease groups that it has formed:

- HIV infection: 225 study participants
- Autoimmune disorder: 159 study participants
- Other immunodeficiencies: 63 study participants
- Infectious diseases without HIV: 34 study participants
- Neoplasia: 88 study participants

The company also provides information on how many study participants in each of these disease groups were included in the presented subpopulation using criteria 1 to 4. However, it does not specify which specific diseases fall into the individual disease groups and to what extent they justify the fulfilment of one or more of the 4 criteria. The individual disease groups are discussed below.

Regarding the disease groups of autoimmune disease and infectious diseases without HIV, it should be noted that according to the RKI, these are not listed among those diseases that are associated with a relevant restriction of the vaccine response.

For the disease groups of other immunodeficiencies and neoplasms, the company does not provide any information on which specific diseases and degrees of severity are involved. It therefore remains unclear how many study participants in the respective disease group have a relevant impairment of the immune system.

Conclusion on the relevance of the submitted subpopulation for the benefit assessment

The information in the company's statement on the characteristics of the included study participants is not sufficient to justify the relevance of the submitted subpopulation for the benefit assessment. It is assumed, as in assessment A23-42, that the majority of people included in the subpopulation do not reflect the research question of this assessment.

Therefore, the submitted subpopulation of the PROVENT study is not used for the benefit assessment. In the following section, the results are presented as supplementary information.

2.1 Supplementary presentation of the PROVENT study

This addendum presents the study listed in the following Table 1.

Table 1: Study pool of the company – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study D8850C00002 (PROVENT[d])	Yes	Yes	No	Yes [6]	Yes [7,8]	Yes [9,10]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the 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.

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

2.2 Study characteristics

The PROVENT study including intervention and study population has already been characterized in dossier assessment A23-42. Appendix B of the dossier assessment includes the corresponding tables.

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

A total of 5254 study participants were randomly assigned to the treatment arms in a 2:1 ratio. 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 [11].

The study's primary outcome was the proportion of study participants with COVID-19 by Day 183. Relevant secondary outcomes were morbidity outcomes and adverse events (AEs). Mortality outcomes were not included as a separate efficacy outcome. The company presented the mortality based on the results of the AEs that lead to death.

According to the study design, the follow-up observation period was 183 or 366 days, depending on the outcome. AE outcomes were further recorded until Day 457.

As per study protocol, the primary analysis was conducted after the occurrence of 24 primary outcome events. This 1st data cut-off was conducted on 5 May 2021. The 2nd data cut-off (29 June 2021), the 3rd data cut-off (29 August 2021) and the 4th data cut-off (13 April 2022) were each conducted as part of a follow-up analysis requested by the regulatory authorities. In the dossier, the company presents analyses on the final data cut-off of 22 February 2023, which was carried out according to the study design after all study participants had completed the last visit on Day 457. The results of this data cut-off are presented below.

Characteristics of the study participants

The characteristics of the study participants in the subpopulation presented by the company are shown in the Appendix of dossier assessment A23-42. They are largely comparable between the study arms of the PROVENT study.

Limitations of the study

As described above, the PROVENT study enrolled only unvaccinated individuals. About 72% of the study participants were vaccinated during the study (71% in the subpopulation presented). However, it cannot be assumed that a complete immunisation according to the recommendations of the RKI consisting of 3 antigen contacts (1 vaccination with at least vaccine 2 doses or infection as well as 1 to 2 booster vaccinations) had already been performed during the expected duration of effect of the PrEP (elimination half-life of about 90 days with subsequent decrease of the protective effect, altogether at least 6 months [11]). Full immunisation is also recommended for persons at relevant risk of inadequate vaccine response [12]. It remains unclear whether the observed effects of the unvaccinated or not fully vaccinated study participants can be transferred without restriction to a fully vaccinated group of individuals.

The PROVENT study was conducted in European countries and the USA between November 2020 and February 2023 and covers the observation period of 457 days (about 15 months) for all study participants. Taking into account the expected duration of the protective effect of PrEP of at least 6 months [11], the period between November 2020 and May 2022 is approximately relevant. During this period, numerous virus variants, including Alpha, Delta and Omikron, were reported as variants of concern [13]. According to the SPC, tixagevimab/cilgavimab has reduced neutralisation activity in vitro against the variants

Omikron BA.1, BA.1.1, BA.4 and BA.5, and has no neutralisation activity in vitro [1,11,14] against the newly emerged variants BQ.1/BQ1.1, BA.4.6, BF.7 and XBB according to the Division of Intensive Care Medicine, Infectious Diseases and Emergency Medicine (COVRIIN), as is described in dossier assessment A23-42. It remains unclear whether the effects observed in the PROVENT study are transferable to individuals who come into contact with one of the virus variants circulating at the time of the benefit assessment, such as BA.5, XBB and their sublines.

Further limitation of the study population

According to the study design, only adults were included in the PROVENT study. The company did not present any data on adolescents aged 12 years and older, nor did it supply an adequate justification of transferability.

Risk of bias across outcomes (study level)

Table 2 shows the risk of bias across outcomes (risk of bias at study level).

Table 2: Risk of bias across outcomes (study level) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of additional aspects	Risk of bias at study level
			Study participants	Treatment providers			
PROVENT	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the PROVENT study is rated as low.

Transferability of the study results to the German health care context

The company assumes that the results of the PROVENT study can be adequately transferred to the German health care context. It justifies this with the comparability of the study population with the risk factors for an insufficient vaccine response defined by the RKI in the German health care context. It states that tixagevimab/cilgavimab is effective against several sublines of the Omicron variant including the Omicron variants BA.2, BA.4 and BA.5. As already described in Section 2.2, this assessment by the company deviates from the information provided in the SPC and the information provided by the COVRIIN expert group, which describe a reduced neutralisation activity against the Omicron variants BA.1, BA.1.1, BA.4 and BA.5.

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

2.3 Results

2.3.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the PROVENT study:

- Mortality
  - all-cause mortality
- Morbidity
  - symptomatic COVID-19 disease
  - severe COVID-19
  - COVID-19 symptoms
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - hypersensitivity reactions and injection site reactions
  - further specific AEs, if any

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

Table 3 shows for which outcomes data were available in the PROVENT study.

Table 3: Matrix of outcomes – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	Outcomes							
	All-cause mortality	symptomatic COVID-19 disease	Severe COVID-19[a]	COVID-19 symptoms[b]	Health-related quality of life	SAEs[c]	Discontinuation due to AEs	Specific AEs
PROVENT	Yes	Yes	Yes	No[d]	No[e]	Yes	Yes	No[f]

a.Severe COVID-19 was defined as the occurrence of pneumonia, hypoxaemia, or a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19.
b. Proportion of study participants with COVID-19-specific symptoms by day 28 after confirmed COVID-19 disease.
e. Overall rate excluding events classified by the company as disease-related; see body of text below for reasons.
d. No suitable data available; see body of text below for reasons.
e. Outcome not recorded.
f. No specific AEs were identified based on the AEs occurring in the study.

AE: adverse event; COVID-19: Coronavirus Disease 2019; RCT: randomized controlled trial; SAE: serious adverse event; WHO: World Health Organisation

Morbidity

Symptomatic COVID-19 disease

In the PROVENT study, the outcome of symptomatic COVID-19 disease is operationalized as the presence of SARS-CoV-2 infection confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) testing with concurrent COVID-19 symptoms. The following symptoms were considered qualifying events regardless of their duration: shortness of breath, difficulty breathing, new-onset confusion (in study participants ≥ 60 years), loss of appetite or reduced food intake (in patients ≥ 60 years), increase in oxygen supply (in study participants with supplemental oxygen demand at baseline). In addition, the following events were considered qualifying for symptomatic disease if they lasted for at least 2 days: chills, cough, fatigue, muscle pain, bodily pain, headache, loss of taste, loss of smell, sore throat, stuffy nose, runny nose, nausea, vomiting, diarrhoea.

In Module 4 A of its dossier, the company presents analysis on Day 183 and Day 366. The predefined primary outcome of symptomatic COVID-19 disease at Day 183 is considered

relevant, since the elimination half-life is about 90 days and thus it can be expected that after Day 183 there is usually no longer a relevant protective effect. The analysis on Day 366 is presented as supplementary information (see Table 5).

Severe COVID-19

The outcome of severe COVID-19 is operationalized as the occurrence of at least one of the following events, in the concurrent presence of RT-PCR-confirmed SARS-CoV-2 infection:

- pneumonia (fever, cough, tachypnoea or dyspnoea and lung infiltrates)
- hypoxaemia (oxygen saturation < 90% in room air and/or severe shortness of breath)
- World Health Organization(WHO) score of 5 or higher on the WHO Clinical Progression Scale for COVID-19 [15]

Since they correspond to severe symptoms, the events included in the outcome are suitable for adequately depicting a severe course of COVID-19. A WHO score of 5 or higher additionally means that affected individuals are hospitalized and require oxygen therapy. Therefore, the results of this operationalization are presented.

In Module 4 A of its dossier, the company also presents analyses on the proportion of study participants with a COVID-19-related stay in the emergency room, as this outcome represents severe symptoms and the resulting burden for the study participants. However, these aspects are already sufficiently taken into account via the outcome of severe COVID-19. Furthermore, the results of the operationalization “proportion of study participants with COVID-19-related stay in the emergency room” are not suitable for the present assessment, as no positive SARS-CoV-2 RT-PCR test had to be available.

COVID-19 symptoms

Study participants who tested positive for SARS-CoV-2 recorded the following COVID-19 symptoms daily until Day 28 of the disease or until resolution of the symptoms:

- Shortness of breath
- Difficulty breathing
- Chills
- Cough
- Fatigue
- Muscle pain
- Bodily pain
- Headache

- Loss of taste
- Loss of smell
- Sore throat
- Stuffy nose
- Runny nose
- Nausea
- Vomiting
- Diarrhoea
- Appetite loss
- Confusion
- Increasing oxygen supply in study participants with supplemental oxygen demand at baseline
- Supplemental oxygen supply

The study participants rated the severity of each of these symptoms on a scale of 0 to 4 (0: not present; 1: mild; 2: moderate; 3: severe; 4: hospitalized). For the relevant subpopulation, the company presented analyses on study participants for each individual symptom who documented a corresponding symptom, regardless of the severity. The analysis presented by the company is not provided in the present addendum. This is justified below.

Compared to the relevant subpopulation, the analysed population is limited, as only those study participants who developed COVID-19 during the course of the study were included in the analysis. This means that it depends on the therapeutic success of the intervention which study participants are included in the analysis. Such a procedure leads to the fact that structural equality ensured by randomization is no longer guaranteed.

Following the hearing, the company submitted additional information on the concomitant medication used in study participants with symptomatic COVID-19 disease. This was similar between the study arms and appears reasonable.

Side effects

SAEs

In Module 4 A, the company presents both overall rates including and excluding events that can be attributed to the symptoms of COVID-19 for the outcomes on side effects. The list of events that the company considers to be symptoms of COVID-19 includes numerous events that in principle adequately represent the symptoms of a COVID-19 disease. However, these

also include events - such as headaches or chills - that can be assigned to both COVID-19 symptoms and side effects. However, this is of no consequence for the subpopulation presented by the company, as the overall rates including and excluding disease-related symptoms are comparable (see Table 5). For the present addendum, the overall SAE rate is used exclusively of the potentially disease-related events.

Severe AEs

In the PROVENT study, the severity of AEs was assessed based on categories defined by the company rather than an established classification. This is not an adequate operationalization of the degree of severity and is disregarded in the benefit assessment.

2.3.2 Risk of bias

Table 4 describes the risk of bias for the results of the relevant outcomes.

Table 4: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study		Outcomes							
	Study level	All-cause mortality	symptomatic COVID-19 disease	Severe COVID-19[a]	COVID-19 symptoms[b]	Health-related quality of life	SAEs[c]	Discontinuation due to AEs[c]	Specific AEs
PROVENT	L	L	L	L	–[d]	–[e]	L	L	–

a. Severe COVID-19 was defined as the occurrence of pneumonia, hypoxaemia, or a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19.
b. Proportion of study participants with COVID-19-specific symptoms by Day 28 after confirmed COVID-19 disease.
c. Overall rate excluding events classified by the company as disease-related.
d. No suitable data available; for the reasoning, see Section 2.3.1 of the present addendum.
e. Outcome not recorded.

AE: adverse event; COVID-19: Coronavirus Disease 2019; L: low; RCT: randomized controlled trial; SAE: serious adverse event; WHO: World Health Organisation

The risk of bias was rated as low for the results of all outcomes presented for which suitable data are available. This assessment concurs with that of the company.

2.3.3 Results

Table 5 summarizes the results on the comparison of tixagevimab/cilgavimab with placebo in study participants of the subpopulation presented by the company. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Table 5: Results (mortality, morbidity, side effects) – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study outcome category outcome	Tixagevimab/cilgavimab		Placebo		Tixagevimab/cilgavimab vs. placebo
	N	individuals with event n (%)	N	individuals with event n (%)	RR [95% CI]; p-value
PROVENT					
Mortality					
All-cause mortality	346	4 (1.2)	173	2 (1.2)	1.00 [0.18; 5.41]; 0.999[a]
Morbidity					
Symptomatic COVID-19 disease by Day 183	346	3 (0.9)	173	8 (4.6)	0.17 [0.05; 0.66]; 0.010[b]
Symptomatic COVID-19 disease by Day 366	346	*22 (6.4)*	173	*19 (11.0)*	*0.54 [0.29; 0.99];* *0.047*[b]
Severe COVID-19[c]	346	0 (0)	173	0 (0)	–
COVID-19 symptoms	No suitable data				
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)[d]	346	251 (72.5)	173	116 (67.1)	–
SAEs[d]	346	32 (9.2)	173	14 (8.1)	1.14 [0.63; 2.08]; 0.736[a]
Discontinuation due to AEs	346	0 (0)	173	0 (0)	–

a. RR, CI (asymptotic) and p-value (Institute's calculation; unconditional exact test, CSZ method according to [16]).
b. RR, CI, p-value: Poisson regression with robust variance; the model includes logarithmic follow-up time as offset and planned treatment group and age (< 60 years vs. ≥ 60 years) as covariates.
c. Operationalized as the occurrence of pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates), hypoxaemia (oxygen saturation < 90% in room air and/or severe shortness of breath), or a score of 5 or higher on the WHO Clinical Progression Scale for COVID-19.
d. Overall rate of only those events that were classified by the company as disease-related. The overall rate of SAEs including events classified by the company as disease-related was 35 (10.1%) in the intervention arm and 18 (10.4%) in the comparator arm.

AE: adverse event; CI: confidence interval; COVID-19: Coronavirus Disease 2019; n: number of study participants with (at least one) event; N: number of analysed study participants; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; WHO: World Health Organization

Mortality

All-cause mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality.

Morbidity

Symptomatic COVID-19 disease

For the outcome of symptomatic COVID-19, a statistically significant difference between treatment groups was found in favour of tixagevimab/cilgavimab.

Severe COVID-19

No events occurred in the outcome of severe COVID-19.

COVID-19 symptoms

No suitable data were available for the outcome of COVID-19 symptoms.

Health-related quality of life

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

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found.

Discontinuation due to AEs

No events occurred in the outcome of discontinuation due to AEs.

Specific AEs

No specific AEs were identified based on the AEs occurring in the study.

2.3.4 Subgroups and other effect modifiers

The present benefit assessment accounts for the following subgroup characteristics:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)

Interaction tests are conducted when at least 10 study participants per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 subgroup.

Presented are only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

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

2.4 Summary

The data subsequently submitted by the company during the commenting procedure do not change the conclusion on the added benefit of tixagevimab/cilgavimab drawn in dossier assessment A23-42 [1].

Table 6 below shows the result of the benefit assessment of tixagevimab/cilgavimab, taking into account dossier assessment A23-42 and the present addendum.

Table 6: Tixagevimab/cilgavimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
PrEP 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-only drugs with monoclonal antibodies for preventive use to protect against COVID-19 at the expense of the SHI system 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 significant 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 social distancing, hygiene measures, mouth-nose coverings) to reduce the risk of infection in all study arms. In cases were 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. 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 G-BA decides on the added benefit.

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Appendix A Results on side effects

For the total rates of AEs and SAEs, the following tables present events for the SOCs and Preferred Terms (PTs) in accordance with MedDRA on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of study participants in 1 study arm
- Overall SAE rates: events which occurred in at least 5% of the study participants in 1 study arm
- in addition, for all events irrespective of severity grade: events which occurred in at least 10 study participants and in at least 1% of study participants in 1 study arm

A complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided for the outcome of discontinuation due to AEs.

The outcome of discontinuation due to AEs is not presented because no events leading to discontinuation occurred.

Table 7: Common AEs[a] – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (multipage table)

Study	**Individuals with event n (%)**	
SOC[b] **PT[b]**	**tixagevimab/cilgavimab** **N = 346**	**placebo** **N = 173**
PROVENT		
Overall AE rate	251 (72.5)	116 (67.1)
Blood and lymphatic system disorders	14 (4.0)	12 (6.9)
Cardiac disorders	16 (4.6)	7 (4.0)
Ear and labyrinth disorders	12 (3.5)	2 (1.2)
Gastrointestinal disorders	85 (24.6)	37 (21.4)
Diarrhoea	34 (9.8)	20 (11.6)
Nausea	28 (8.1)	11 (6.4)
General disorders and administration site conditions	110 (31.8)	39 (22.5)
Fatigue	56 (16.2)	20 (11.6)
Fever	29 (8.4)	9 (5.2)
Pain	23 (6.6)	11 (6.4)
Chills	23 (6.6)	7 (4.0)
Asthenia	11 (3.2)	4 (2.3)
Infections and infestations	130 (37.6)	57 (32.9)
COVID-19	43 (12.4)	24 (13.9)
Urinary tract infection	16 (4.6)	11 (6.4)
Injury, poisoning and procedural complications	45 (13.0)	21 (12.1)
Postvaccinal complication	13 (3.8)	7 (4.0)
Investigations	24 (6.9)	11 (6.4)
Metabolism and nutrition disorders	36 (10.4)	12 (6.9)
Decreased appetite	14 (4.0)	4 (2.3)
Musculoskeletal and connective tissue disorders	74 (21.4)	38 (22.0)
Myalgia	25 (7.2)	11 (6.4)
Arthralgia	18 (5.2)	5 (2.9)
Back pain	15 (4.3)	5 (2.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	15 (4.3)	5 (2.9)
Nervous system disorders	91 (26.3)	39 (22.5)
Headache	55 (15.9)	26 (15.0)
Psychiatric disorders	17 (4.9)	8 (4.6)
Renal and urinary disorders	20 (5.8)	7 (4.0)

Table 7: Common AEs[a] – RCT, direct comparison: tixagevimab/cilgavimab versus placebo (multipage table)

Study	**Individuals with event n (%)**	
SOC[b] **PT[b]**	**tixagevimab/cilgavimab N = 346**	**placebo N = 173**
Respiratory, thoracic and mediastinal disorders	101 (29.2)	42 (24.3)
Cough	51 (14.7)	25 (14.5)
Rhinorrhoea	41 (11.8)	17 (9.8)
Oropharyngeal pain	37 (10.7)	16 (9.2)
Nasal congestion	35 (10.1)	13 (7.5)
Dyspnoea	25 (7.2)	12 (6.9)
Skin and subcutaneous tissue disorders	34 (9.8)	16 (9.2)
Vascular disorders	32 (9.2)	11 (6.4)
Hypertension	20 (5.8)	8 (4.6)

a. Events that occurred in ≥ 10 study participants in at least one study arm.
b. MedDRA version 24.0; SOC and PT notation taken from Module 4.

AE: adverse event; Coronavirus Disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of study participants with at least 1 event; N: number of analysed study participants; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 8: Common SAEs[a] – RCT, direct comparison: tixagevimab/cilgavimab versus placebo

Study	**Individuals with event n (%)**	
SOC[b] **PT[b]**	**Tixagevimab/cilgavimab N = 346**	**Placebo N = 173**
PROVENT		
Overall SAE rate	35 (10.1)	18 (10.4)
Infections and infestations	12 (3.5)	11 (6.4)

a. Events that occurred in ≥ 10 study participants in the intervention arm, or in ≥ 5 % of patients in the comparator arm.
b. MedDRA version 24.0; SOC and PT notation taken from Module 4.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of study participants with at least 1 event; N: number of analysed study participants; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class