Sipavibart
(pre-exposure prophylaxis of COVID-19)

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

EXTRACT

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Medical and scientific advice

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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 5 people.

IQWiG thanks the respondents and the patient organization “Deutsche Rheuma-Liga Bundesverband e. V.” for participating in the written exchange and for their support. The respondents and the “Deutsche Rheuma-Liga Bundesverband e. V.” were 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
AE	adverse event
BMI	body mass index
CAR	chimeric antigen receptor
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
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)
RCT	randomized controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SPC	Summary of Product Characteristics
STIKO	Ständige Impfkommission (Standing Committee on Vaccination)
VOC	variant of concern

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 sipavibart. 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 13 February 2025.

Research question

The aim of this report is to assess the added benefit of sipavibart in comparison with watchful waiting as the appropriate comparator therapy (ACT) for pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments.

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 for pre-exposure prophylaxis of COVID-19 at the expense of the statutory health insurance (SHI). This concerns those individuals in whom (1) for medical reasons (e.g. congenital or acquired immunodeficiencies, underlying diseases or immunosuppressive therapies) no or no sufficient immune protection against COVID-19 can be achieved by vaccination, or in whom (2) vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cannot be carried out due to a contraindication, and who are thus exposed to an increased risk of progressing to severe COVID-19.

The research question presented in Table 2 was defined in accordance with the ACT specified by the G-BA and the information provided in COVID-19 Prevention Ordinance §2.

Table 2: Research question for the benefit assessment of sipavibart

Therapeutic indication	**ACT**[a]
Pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments[b, c, d, e, f]	Watchful waiting

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, sipavibart should be used according to official recommendations, if available, and based on information on the activity of sipavibart against currently circulating virus variants.
c. According to §2 of the COVID-19 Prevention Ordinance, entitlement to the provision of prescription drugs for pre-exposure prophylaxis of COVID-19 at the expense of the SHI only exists for insured persons if, for medical reasons, no or no sufficient immune protection against COVID-19 can be achieved by vaccination, or if vaccinations against SARS-CoV-2 coronavirus cannot be carried out due to a contraindication, and they are thus exposed to an increased risk of progressing to severe COVID-19. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
d. It is assumed that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, general hygiene measures) to reduce the risk of infection.
e. 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.
f. 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; VOC: variant of concern

The company followed the G-BA's ACT. At the same time, the company argued that the administration of drugs (such as tixagevimab/cilgavimab), for which no important effect on the outcomes presented was to be expected, also constituted implementation of the comparator therapy specified by the G-BA, i.e. watchful waiting. For its assessment, the company therefore considered not only the comparison with placebo but also the comparison with tixagevimab/cilgavimab. The company's approach is not appropriate, as the administration of tixagevimab/cilgavimab cannot be equated with watchful waiting.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

Neutralizing activity against SARS-CoV-2 variants

According to the Summary of Product Characteristics (SPC), sipavibart should be used in accordance with official recommendations, if available, and based on information on the activity of sipavibart against currently circulating virus variants. According to the SPC, sipavibart lacks in vitro neutralization activity against SARS-CoV-2 variants that contain F456L mutations in the spike protein. These include, among others, the LP.8.1 and XEC lines, which were predominantly circulating at the time of this benefit assessment. The SPC states that due

to the absence of in vitro neutralizing activity, sipavibart is not anticipated to provide any protection against symptomatic COVID-19 in virus variants with F456L mutations.

Results

A review of the completeness of the study pool for the direct comparison of sipavibart with the ACT watchful waiting did not identify any RCTs beyond the SUPERNOVA and NOVELLA RCTs, consistent with the findings of the company.

In its dossier, the company presented analyses of a subpopulation for each of the SUPERNOVA and NOVELLA studies that was eligible for pre-exposure prophylaxis against COVID-19 on the basis of the COVID-19 Prevention Ordinance §2. The analyses of both studies presented by the company were unsuitable for the present benefit assessment, however. For the SUPERNOVA study, this is due to the fact that the company also considered in its analyses people who were treated with tixagevimab/cilgavimab instead of watchful waiting in the comparator arm of the study. The main reason for the exclusion of the NOVELLA study was that the study was conducted in a different health care context. Overall, therefore, no suitable data were available from either study for the comparison of sipavibart with watchful waiting. The SUPERNOVA and NOVELLA studies are described below and an explanation provided as to why the data presented were unsuitable for the benefit assessment.

Evidence presented by the company – SUPERNOVA study

The SUPERNOVA study is an ongoing phase 1 to 3 study on COVID-19 pre-exposure prophylaxis. The double-blind part of the study (phase 3, main cohort) investigated the comparison of sipavibart with tixagevimab/cilgavimab or placebo for COVID-19 pre-exposure prophylaxis in immunocompromised adults and adolescents aged 12 years and older. Included were adults and adolescents 12 years of age and older weighing ≥ 40 kg who were immunocompromised due to a medical condition or receipt of immunosuppressive treatments.

In the SUPERNOVA study, 2 treatments (Day 1 and Day 181) with the study medication were planned. Treatment started in both study arms with the administration of a first dose of the respective study medication for pre-exposure prophylaxis on Day 1. At the beginning of the study, treatment in the control group was carried out with the antibody combination tixagevimab/cilgavimab in accordance with the study design. With a global amendment to the study protocol (Amendment 6 dated 14 June 2023), the study design was adjusted and placebo was specified as the study medication in the control group instead of tixagevimab/cilgavimab. As a result, people who were included in the study up to Amendment 6 to the protocol received tixagevimab/cilgavimab as the first dose in the comparator arm of the study, and people who were included after this amendment received placebo. In the overall study population, 1105 (66%) of the people treated in the comparator

arm received tixagevimab/cilgavimab and 561 people (34%) received placebo as the first dose. A second dose of the respective study medication for pre-exposure prophylaxis was additionally planned for Day 181. However, since no one had received a second dose at the time of Amendment 6 to the protocol, only placebo was administered as the second dose in the comparator arm.

A total of 3349 people were randomly assigned to the 2 treatment arms in a 1:1 ratio in the SUPERNOVA study. For its assessment, the company used analyses of a subpopulation of the study for which pre-exposure prophylaxis against COVID-19 was an option. This comprised 548 people in the intervention arm and 525 people in the comparator arm.

The analyses of the SUPERNOVA study presented by the company are unsuitable for the benefit assessment

The analyses of the subpopulation of the SUPERNOVA study presented by the company are unsuitable for drawing conclusions on the added benefit of sipavibart in comparison with the ACT. This is mainly due to the fact that the company's analyses also included study participants in the comparator arm who received tixagevimab/cilgavimab and thus active therapy instead of watchful waiting, the comparator therapy specified by the G-BA.

Tixagevimab/cilgavimab does not correspond to the comparator therapy of watchful waiting specified by the G-BA

In the SUPERNOVA study, participants in the comparator arm who were included prior to Amendment 6 to the protocol received tixagevimab/cilgavimab as the comparator therapy. In Module 4 A of the dossier, the company presented analyses for a subpopulation of the SUPERNOVA study which considered not only people who were included after Amendment 6 and thus received placebo as the comparator therapy (for those allocated to the comparator arm), but also people included before this amendment. The company argued that due to insufficient in vitro neutralization activity and unproven clinical efficacy against virus variants during the study, the temporary administration of tixagevimab/cilgavimab in the comparator arm did not lead to a distortion of the results in terms of the benefit assessment. The company also argued that in any case, if tixagevimab/cilgavimab were clinically effective, the efficacy outcomes would be influenced to the disadvantage of sipavibart. It stated that a relevant bias due to the temporary administration of tixagevimab/cilgavimab in the comparator arm could also be ruled out for the safety analyses. The company added that tixagevimab/cilgavimab has a very good safety profile according to the corresponding benefit assessment, as there were no clinically relevant treatment differences to the disadvantage of tixagevimab/cilgavimab compared with placebo in either therapeutic indication of this drug combination (COVID-19 pre-exposure prophylaxis and treatment of COVID-19).

The company's reasoning is not appropriate. It cannot be concluded from the available evidence on tixagevimab/cilgavimab that the administration of this drug combination in this therapeutic indication is equivalent to the administration of placebo.

Based on the results of the PROVENT study, tixagevimab/cilgavimab was approved for COVID-19 pre-exposure prophylaxis at a dose of 150 mg per antibody. In the SUPERNOVA study, however, tixagevimab/cilgavimab was given at a dosage twice this – at 300 mg per antibody. It therefore cannot be inferred from the results of the PROVENT study comparing tixagevimab/cilgavimab with placebo that treatment in the SUPERNOVA study with the active drug combination tixagevimab/cilgavimab can be equated with treatment with placebo for either benefit or harm outcomes. Furthermore, the PROVENT study was not used in the benefit assessment of tixagevimab/cilgavimab for the assessment of an added benefit of tixagevimab/cilgavimab as COVID-19 pre-exposure prophylaxis, as the available data were not sufficient to justify a therapeutic indication for COVID-19 pre-exposure prophylaxis for the subpopulation of the PROVENT study presented in this procedure. Against this background, it remains unclear whether the subpopulation of the PROVENT study presented at that time is comparable with the subpopulation of the SUPERNOVA study with a therapeutic indication for COVID-19 pre-exposure prophylaxis presented by the company in the current procedure. Furthermore, the time periods in which the PROVENT (11/2020 to 2/2023) and SUPERNOVA (3/2023 to data cut-off in 3/2024) studies were conducted differ, so that an argument for equating treatment with tixagevimab/cilgavimab and placebo based on the results of the PROVENT study is also problematic given the different COVID-19 contexts in the respective study periods.

The approval of tixagevimab/cilgavimab for the treatment of COVID-19 was based on the results of the TACKLE study. The results of the TACKLE study are also not suitable for demonstrating that treatment with tixagevimab/cilgavimab is equivalent to treatment with placebo in this therapeutic indication, as adults with no restrictions in terms of immunodeficiency who also already had acute COVID-19 were examined.

Overall, it cannot be concluded from the PROVENT and TACKLE studies on tixagevimab/cilgavimab that treatment with this active drug combination can be equated with treatment with placebo. The company did not provide any information on how many people in the subpopulation of the SUPERNOVA study it analysed received tixagevimab/cilgavimab as the study medication in the comparator arm. However, based on a proportion of 66% of people in the total population of the study, it can be assumed that this affected a relevant proportion of people in the comparator arm of the subpopulation. The analyses of the study presented by the company are therefore unsuitable for the present benefit assessment. In principle, it would have been possible for the company to present analyses for the SUPERNOVA study of a subpopulation in which only participants randomized from

Amendment 6 to the protocol onwards were considered, in order to investigate the comparison relevant for this assessment.

Further uncertainties or shortcomings regarding the SUPERNOVA study analyses presented by the company

Irrespective of the fact that the administration of tixagevimab/cilgavimab in the SUPERNOVA study does not correspond to the ACT of watchful waiting, the analyses presented by the company in Module 4 A of the dossier are also subject to further uncertainties or shortcomings relating in particular to the following aspects: the transferability of the results to a fully immunized group of people, the therapeutic indication for a second dose of pre-exposure prophylaxis and the events or data collection periods considered in the analyses.

Evidence presented by the company – NOVELLA study

The NOVELLA study is a double-blind RCT comparing sipavibart with placebo for COVID-19 pre-exposure prophylaxis in adults with diseases or co-morbidities that can lead to an impaired immune response after vaccination and who are therefore at high risk of progressing to severe COVID-19.

The study was only conducted in Russian study centres. A total of 116 adults were randomly assigned in a 3:1 ratio to treatment with sipavibart (N = 87) or placebo (N = 29). In Appendix 4 G to Module 4 A of the dossier, the company presented analyses of the NOVELLA study for a subpopulation with a therapeutic indication for COVID-19 pre-exposure prophylaxis, comprising 15 people in the intervention arm and 11 people in the comparator arm. The company presented these analyses solely as supplementary information and did not consider the NOVELLA study for its derivation of added benefit.

NOVELLA study unsuitable for the benefit assessment

The NOVELLA study is unsuitable for this benefit assessment. This is in particular due to the fact that the NOVELLA study was conducted in a different health care context. The study was conducted exclusively at study centres in Russia and thus under COVID-19 regulations in this health care context. This had a particular impact on the immunization status of the adults included. Only about half of the people in the subpopulation presented by the company were vaccinated against SARS-CoV-2 before the start of the study, using the Sputnik V/Sputnik Light vaccine, which is not approved in the European Union. For those individuals who were not vaccinated against SARS-CoV-2 before the start of the study, no information was available as to why this was the case. For these people, it is therefore unclear whether they were eligible for pre-exposure prophylaxis in accordance with §2 of the COVID-19 Prevention Ordinance. Previous confirmed COVID-19 infections were also only present in some of the people in the subpopulation presented by the company (65%). It therefore cannot be assumed that the

adults included in the study had developed basic immunity in accordance with the Standing Committee on Vaccination (STIKO) recommendations.

In the German health care context the STIKO recommends that independent of the use of drugs for pre-exposure prophylaxis, people with immunodeficiency should first build up a basic immunity (consisting of at least 3 contacts with the pathogen, at least one of which should be a vaccination), and that they receive annual booster vaccinations against SARS-CoV-2. The vaccines recommended in this context also differ from the vaccines used in the NOVELLA study. Against the background of these fundamental differences, it is not assumed that the study provides informative data for the German health care context. The company's approach of not utilizing the NOVELLA study for its assessment is therefore considered appropriate.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of sipavibart 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]

Table 3 presents a summary of the probability and extent of the added benefit of sipavibart.

[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: Sipavibart – 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 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments[b, c, d, e, f]	Watchful waiting	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, sipavibart should be used according to official recommendations, if available, and based on information on the activity of sipavibart against currently circulating virus variants.
c. According to §2 of the COVID-19 Prevention Ordinance, entitlement to the provision of prescription drugs for pre-exposure prophylaxis of COVID-19 at the expense of the SHI only exists for insured persons if, for medical reasons, no or no sufficient immune protection against COVID-19 can be achieved by vaccination, or if vaccinations against SARS-CoV-2 coronavirus cannot be carried out due to a contraindication, and they are thus exposed to an increased risk of progressing to severe COVID-19. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
d. It is assumed that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, general hygiene measures) to reduce the risk of infection.
e. 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.
f. 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; VOC: variant of concern

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of sipavibart in comparison with watchful waiting as the ACT for pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments.

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 for pre-exposure prophylaxis of COVID-19 at the expense of the SHI. This concerns those individuals in whom (1) for medical reasons (e.g. congenital or acquired immunodeficiencies, underlying diseases or immunosuppressive therapies) no or no sufficient immune protection against COVID-19 can be achieved by vaccination, or in whom (2) vaccinations against SARS-CoV-2 cannot be carried out due to a contraindication, and who are thus exposed to an increased risk of progressing to severe COVID-19.

The research question presented in Table 4 was defined in accordance with the ACT specified by the G-BA and the information provided in COVID-19 Prevention Ordinance §2.

Table 4: Research question for the benefit assessment of sipavibart

Therapeutic indication	**ACT[a]**
Pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments[b, c, d, e, f]	Watchful waiting

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, sipavibart should be used according to official recommendations, if available, and based on information on the activity of sipavibart against currently circulating virus variants.
c. According to §2 of the COVID-19 Prevention Ordinance, entitlement to the provision of prescription drugs for pre-exposure prophylaxis of COVID-19 at the expense of the SHI only exists for insured persons if, for medical reasons, no or no sufficient immune protection against COVID-19 can be achieved by vaccination, or if vaccinations against SARS-CoV-2 coronavirus cannot be carried out due to a contraindication, and they are thus exposed to an increased risk of progressing to severe COVID-19. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
d. It is assumed that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, general hygiene measures) to reduce the risk of infection.
e. 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.
f. 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; VOC: variant of concern

The company followed the G-BA's ACT. At the same time, the company argued that the administration of drugs (such as tixagevimab/cilgavimab), for which no important effect on the outcomes presented was to be expected, also constituted implementation of the comparator therapy specified by the G-BA, i.e. watchful waiting. For its assessment, the company therefore considered not only the comparison with placebo but also the comparison with tixagevimab/cilgavimab. The company's approach is not appropriate, as the administration of tixagevimab/cilgavimab cannot be equated with watchful waiting. This is explained in more detail in Chapter I 3 as part of the assessment of the evidence presented by the company.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurs with the company's inclusion criteria.

Neutralizing activity against SARS-CoV-2 variants

According to the SPC [4], sipavibart should be used in accordance with official recommendations, if available, and based on information on the activity of sipavibart against currently circulating virus variants. According to the SPC, sipavibart lacks in vitro neutralization activity against SARS-CoV-2 variants that contain F456L mutations in the spike protein. These include, among others, the LP.8.1 and XEC lines, which were predominantly circulating at the time of this benefit assessment [5,6]. The SPC states that due to the absence of in vitro neutralizing activity, sipavibart is not anticipated to provide any protection against symptomatic COVID-19 in virus variants with F456L mutations.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on sipavibart (status: 16 December 2024)
- Bibliographical literature search on sipavibart (last search on 16 December 2024)
- Search of trial registries/trial results databases for studies on sipavibart (last search on 16 December 2024)
- Search on the G-BA website for sipavibart (last search on 17 December 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on sipavibart (last search on 10 March 2025); for search strategies, see I Appendix A of the full dossier assessment

The company identified the RCTs SUPERNOVA [7-12] and NOVELLA [13] for the direct comparison of sipavibart with the ACT watchful waiting. The review of the completeness of the study pool did not identify any additional RCTs.

In its dossier, the company presented analyses of a subpopulation for each of the SUPERNOVA and NOVELLA studies that was eligible for pre-exposure prophylaxis against COVID-19 on the basis of the COVID-19 Prevention Ordinance §2. However, for its assessment it used only the analyses of the SUPERNOVA study, while the analyses for the NOVELLA study were merely presented as a supplement in Appendix 4 G of Module 4 A of the dossier. The analyses of both studies presented by the company were unsuitable for the present benefit assessment, however. For the SUPERNOVA study, this is due to the fact that the company also considered in its analyses people who were treated with tixagevimab/cilgavimab instead of watchful waiting in the comparator arm of the study (see Chapter I 2). The main reason for the exclusion of the NOVELLA study was that the study was conducted in a different health care context. Overall, therefore, no suitable data were available from either study for the comparison of sipavibart with watchful waiting. The SUPERNOVA and NOVELLA studies are described below and an explanation provided as to why the data presented were unsuitable for the benefit assessment.

Evidence presented by the company – SUPERNOVA study

The SUPERNOVA study is an ongoing phase 1 to 3 study on COVID-19 pre-exposure prophylaxis, which comprises 2 cohorts and a substudy, each to be analysed separately. The sentinel safety cohort (phase 1) compared sipavibart in combination with cilgavimab versus placebo in healthy adults. In the substudy (phase 2), sipavibart at an unauthorized dose of

1200 mg was compared with tixagevimab/cilgavimab in healthy or immunocompromised adults. Both the sentinel safety cohort and the substudy were not relevant for the benefit assessment due to the difference in population or dosage and are therefore not described in more detail below.

The double-blind part (phase 3, main cohort) of the SUPERNOVA study investigated the comparison of sipavibart with tixagevimab/cilgavimab or placebo for COVID-19 pre-exposure prophylaxis in immunocompromised adults and adolescents aged 12 years and older. Included were adults and adolescents 12 years of age and older weighing ≥ 40 kg who were immunocompromised due to a medical condition or receipt of immunosuppressive treatments. In the SUPERNOVA study, immunodeficiency was defined by the presence of one of the following criteria at baseline: solid tumour and active immunosuppressive treatment, haematological malignancy, active use of immunosuppressive drugs, received chimeric antigen receptor (CAR) T-cell therapy, received B-cell-depleting therapies within the last year, moderate or severe primary or secondary immunodeficiency, advanced or untreated human immunodeficiency virus (HIV) infection or solid organ transplantation within the last 2 years and/or haematopoietic stem cell transplantation within the last 2 years and/or chronic graft-versus-host disease. The inclusion criteria of the study did not state any specific requirements regarding vaccination status against SARS-CoV-2. However, no vaccination should have been administered within 3 months prior to the first administration of the study medication. People who had COVID-19 within this period were also excluded from participation in the study.

In the SUPERNOVA study, 2 treatments (Day 1 and Day 181) with the study medication were planned. Treatment started in both study arms with the administration of a first dose of the respective study medication for pre-exposure prophylaxis on Day 1. At the beginning of the study, treatment in the control group was carried out with the antibody combination tixagevimab/cilgavimab in accordance with the study design. With a global amendment to the study protocol (Amendment 6 dated 14 June 2023), the study design was adjusted and placebo was specified as the study medication in the control group instead of tixagevimab/cilgavimab. As a result, people who were included in the study up to Amendment 6 to the protocol received tixagevimab/cilgavimab as the first dose in the comparator arm of the study; and people who were included after this amendment received placebo. In the overall study population, 1105 (66%) of the people treated in the comparator arm received tixagevimab/cilgavimab and 561 people (34%) received placebo as the first dose. In the SUPERNOVA study, an on-label dosage of sipavibart was administered intramuscularly; alternatively, administration as an intravenous infusion is also an option according to the SPC [4]. The dosage of tixagevimab/cilgavimab in the SUPERNOVA study was 300 mg per antibody as an intramuscular injection, twice the dosage approved for COVID-19 pre-exposure prophylaxis [14]. The placebo was administered intramuscularly.

In addition to the administration of the study medication on Day 1, a second dose of the respective study medication was also administered on Day 181 for pre-exposure prophylaxis, provided that the following criteria were met at this time: negative SARS-CoV-2 antigen test, body weight ≥ 40 kg, negative pregnancy test, no administration of immunoglobulins within the last 6 months, no SARS-CoV-2 vaccination and no administration of other drugs for the prophylaxis of COVID-19 within the last 14 days. Since no one had received a second dose at the time of Amendment 6 to the protocol, only placebo was administered as the second dose in the comparator arm.

A total of 3349 people were randomly assigned to the 2 treatment arms in a 1:1 ratio in the SUPERNOVA study. Stratification was based on the factors SARS-CoV-2 vaccination within 6 months prior to randomization, administration of tixagevimab/cilgavimab within 12 months prior to randomization, and SARS-CoV-2 infection within 6 months prior to randomization. For its assessment, the company used analyses of a subpopulation of the study for which pre-exposure prophylaxis against COVID-19 was an option (for details, see the following text section). This comprised 548 people in the intervention arm and 525 people in the comparator arm.

Co-primary outcomes of the SUPERNOVA study were confirmed symptomatic COVID-19 by Day 361 – once for infection with any SARS-CoV-2 variant and once for infection with virus variants without F456L mutation in the spike protein. Furthermore, analyses of outcomes in the side effects category were also listed under the primary outcome criteria of the study. Patient-relevant secondary outcomes were outcomes on morbidity. Health-related quality of life outcomes were not recorded in the SUPERNOVA study.

In its dossier, the company presented analyses of the 29 March 2024 data cut from the SUPERNOVA study. This was the prespecified data cut-off for the primary analysis after reaching a median observation period of > 181 days, ≥ 43 symptomatic COVID-19 cases with a virus variant without F456-L mutation and ≥ 199 symptomatic COVID-19 cases of any virus variant. At the point of data cut-off, all study participants had received the first dose of study medication and, unless they had discontinued the study prematurely, had achieved a follow-up observation period of at least 90 days after the first dose of study medication. In the total study population, a second dose of the study medication was received by 53% of the study participants in each of the 2 study arms.

For a characterization of the study, see also I Appendix B of the full dossier assessment.

Approach of the company to identify individuals with a therapeutic indication for COVID-19 pre-exposure prophylaxis is adequate

From the total population of the SUPERNOVA study, the company formed a subpopulation of those study participants who in its opinion, according to the criteria of §2 of the COVID-19

Prevention Ordinance, were entitled to the provision of prescription drugs for pre-exposure prophylaxis of COVID-19 at the expense of the SHI system. According to §2 of the COVID-19 Prevention Ordinance, individuals 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 SARS-CoV-2 coronavirus due to a contraindication and are thus at increased risk of progressing to severe COVID-19, are eligible for treatment [3].

Based on the recommendation on COVID-19 pre-exposure prophylaxis by the STIKO [15], the company used medical criteria to define the population of the SUPERNOVA study who were entitled to reimbursement according to the COVID-19 Prevention Ordinance (referred to as the prescription population in Module 4 A). It included those people who fulfilled at least one of the following criteria at baseline:

- CAR T-cell therapy
- Solid organ transplantation
- Haematopoietic stem cell transplantation
- Moderate or severe primary immunodeficiency
- B-cell depletion therapy within 1 year prior to study inclusion
- Malignant solid tumour disease under ongoing chemotherapy
- Haematological malignancy under ongoing chemotherapy

These criteria largely correspond to the criteria for people for whom the STIKO recommends COVID-19 pre-exposure prophylaxis with the antibody combination tixagevimab/cilgavimab in addition to SARS-CoV-2 vaccination [15]. Due to the reduced and possibly completely absent neutralization capacity of tixagevimab/cilgavimab against some SARS-CoV-2 sublines, this combination should only be considered in justified individual cases according to the STIKO. Justified individual cases may be individuals with an expected or proven severe limitation to the immune response to SARS-CoV-2 vaccination, such as those

- after autologous or allogeneic stem cell transplantation before immunological reconstitution,
- under or after therapy with anti-B-cell antibodies, if no reconstitution of the B-cell capacities has taken place,
- under CAR T-cell therapy,
- under strong immunosuppression, e.g. after transplantation of a solid organ or under ongoing chemotherapy,

- with genetic immunodeficiencies that impair antiviral immunity.

The STIKO recommendations explicitly refer to COVID-19 pre-exposure prophylaxis with the antibody combination tixagevimab/cilgavimab. However, since according to the SPC [4] it can be assumed that sipavibart, like tixagevimab/cilgavimab, has no in vitro neutralization capacity against the currently circulating SARS-CoV-2 variants (see Chapter I 2), it is assumed that the conditions formulated by the STIKO for tixagevimab/cilgavimab for use in justified exceptional cases should also be applied to the use of sipavibart. Against this background, the company's procedure for identifying people with a therapeutic indication for COVID-19 pre-exposure prophylaxis in the SUPERNOVA study is considered appropriate.

The analyses of the SUPERNOVA study presented by the company are unsuitable for the benefit assessment

The analyses of the previously described subpopulation presented by the company in its dossier are unsuitable for drawing conclusions on the added benefit of sipavibart in comparison with the ACT. This is mainly due to the fact that the company's analyses also included study participants in the comparator arm who received tixagevimab/cilgavimab and thus active therapy instead of watchful waiting, the comparator therapy specified by the G-BA. This is further explained below. In addition, there are further shortcomings and uncertainties in the analyses presented by the company, which are also then discussed.

Tixagevimab/cilgavimab does not correspond to the comparator therapy of watchful waiting specified by the G-BA

In the SUPERNOVA study, participants in the comparator arm who were included prior to Amendment 6 to the protocol received tixagevimab/cilgavimab as the comparator therapy. Only with this amendment was the comparator therapy used in the study changed to placebo, so that people subsequently included and assigned to the comparator arm received placebo as the comparator therapy (see previous description of the SUPERNOVA study design).

In Module 4 A of the dossier, the company presented analyses for the previously described subpopulation of the SUPERNOVA study with a therapeutic indication for COVID-19 pre-exposure prophylaxis. However, it did not consider only those people who were included in the study after Amendment 6 to the protocol and thus received placebo as the comparator therapy when allocated to the comparator arm, but instead also considered those people included before the amendment who received tixagevimab/cilgavimab in the comparator arm. The company argued that due to insufficient in vitro neutralization activity and unproven clinical efficacy against virus variants during the study, the temporary administration of tixagevimab/cilgavimab in the comparator arm did not lead to a distortion of the results in terms of the benefit assessment. The company also argued that in any case, if tixagevimab/cilgavimab were clinically effective, the efficacy outcomes would be influenced

to the disadvantage of sipavibart. It stated that a relevant bias due to the temporary administration of tixagevimab/cilgavimab in the comparator arm could also be ruled out for the safety analyses. The company added that tixagevimab/cilgavimab has a very good safety profile according to the corresponding benefit assessment, as there were no clinically relevant treatment differences to the disadvantage of tixagevimab/cilgavimab compared with placebo in either therapeutic indication of this drug combination (COVID-19 pre-exposure prophylaxis and treatment of COVID-19).

The company's reasoning is not appropriate. It cannot be concluded from the available evidence on tixagevimab/cilgavimab that the administration of this drug combination is equivalent to the administration of placebo in this therapeutic indication. Based on the results of the PROVENT study [16], tixagevimab/cilgavimab was approved for COVID-19 pre-exposure prophylaxis at a dose of 150 mg per antibody [14]. In the SUPERNOVA study, however, tixagevimab/cilgavimab was given at a dosage twice this – at 300 mg per antibody. It therefore cannot be inferred from the results of the PROVENT study comparing tixagevimab/cilgavimab with placebo that treatment in the SUPERNOVA study with the active drug combination tixagevimab/cilgavimab can be equated with treatment with placebo for either benefit or harm outcomes. Additionally, in the context of the benefit assessment of tixagevimab/cilgavimab (dossier assessment A23-42 [17] and addendum A23-96 [18] as well as the associated G-BA procedure [19]) the PROVENT study was not used for the assessment of the added benefit of tixagevimab/cilgavimab as COVID-19 pre-exposure prophylaxis, as the available information was not sufficient to justify a therapeutic indication for COVID-19 pre-exposure prophylaxis for the subpopulation of the PROVENT study presented in this procedure. Against this background, it remains unclear whether the subpopulation of the PROVENT study presented at that time is comparable with the subpopulation of the SUPERNOVA study with a therapeutic indication for COVID-19 pre-exposure prophylaxis presented by the company in the current procedure. Furthermore, the time periods in which the PROVENT (11/2020 to 2/2023) and SUPERNOVA (3/2023 to data cut-off in 3/2024) studies were conducted differ, so that an argument for equating treatment with tixagevimab/cilgavimab and placebo based on the results of the PROVENT study is also problematic given the different COVID-19 contexts in the respective study periods.

The approval of tixagevimab/cilgavimab for the treatment of COVID-19 was based on the results of the TACKLE study [20] (dossier assessment A22-111 [21]). In this study, the drug combination was used at a dosage of 300 mg per antibody, but in adults with no restrictions regarding immunodeficiency who also already had acute COVID-19. Therefore, the results of the TACKLE study are also not suitable for demonstrating that treatment with tixagevimab/cilgavimab is equivalent to treatment with placebo in this therapeutic indication.

Overall, it cannot be concluded from the PROVENT and TACKLE studies on tixagevimab/cilgavimab that treatment with this active drug combination can be equated with treatment with placebo. The company did not provide any information on how many people in the subpopulation of the SUPERNOVA study it analysed received tixagevimab/cilgavimab as the study medication in the comparator arm. However, based on a proportion of 66% of people in the total population of the study, it can be assumed that this affected a relevant proportion of people in the comparator arm of the subpopulation. The analyses of the study presented by the company are therefore unsuitable for the present benefit assessment. In principle, it would have been possible for the company to present analyses for the SUPERNOVA study of a subpopulation in which only participants randomized from Amendment 6 to the protocol onwards were considered, in order to investigate the comparison relevant for this assessment.

Further comments on SUPERNOVA study analyses presented by the company

Irrespective of the fact that the administration of tixagevimab/cilgavimab in the SUPERNOVA study does not correspond to the ACT watchful waiting, the analyses presented by the company in Module 4 A of the dossier also have the following further uncertainties or shortcomings:

Transferability of the results of the company's subpopulation is unclear

The recommendations on pre-exposure prophylaxis described above should be observed in justified exceptional cases in the present therapeutic indication only in addition to the STIKO recommendations on SARS-CoV-2 vaccination. In principle, the STIKO recommends that people with immunodeficiency first build up basic immunity (consisting of at least 3 contacts with the pathogen, at least one of which should be a vaccination), and that they receive annual booster vaccinations against SARS-CoV-2 [22]. The company provided no information in the dossier on the extent to which these recommendations were implemented in the subpopulation of the SUPERNOVA study it presented. The electronic case report form shows that at baseline, in addition to information on whether there had been infections with SARS-CoV-2 in the past, information was also collected on whether vaccinations against SARS-CoV-2 had been given in the past. Not only infections or vaccinations within the last 6 months were recorded. For vaccinations, in addition to the date of the last vaccination, details of the vaccine administered and the dose number were also recorded (in categories from 1st to > 5th dose). This means that comprehensive information on the immunization of the included individuals is available, which the company did not process for the subpopulation it presented in Module 4 A of the dossier. Based on the start date of the SUPERNOVA study in 2023, it can be assumed that a large proportion of the study population had already received SARS-CoV-2 vaccinations or experienced infections. However, as detailed information on the vaccination status and previous infections of the people in the subpopulation is missing, it remains unclear whether

the observed effects from the analyses presented by the company would be applicable to a fully immunized group of people.

The relevance of the second dose of the study medication to the benefit assessment is unclear

As described above, in Module 4 A the company presented results for the subpopulation comprising people with a therapeutic indication for COVID-19 pre-exposure prophylaxis. The criteria for the therapeutic indication were based on patient characteristics at baseline. The company did not explain to what extent these criteria were also fulfilled at the time of the second administration of the study medication (6 months after administration of the first dose). It therefore remains unclear whether at the time of the second dose there was still a therapeutic indication for COVID-19 pre-exposure prophylaxis for those included in the subpopulation. Whether information was collected in the study on the basis of which it can be assessed whether a therapeutic indication still existed also remains unclear considering the information available in the dossier. If a therapeutic indication for COVID-19 pre-exposure prophylaxis cannot be confirmed for the majority of the relevant subpopulation at the time of the second dose, the analyses that are relevant for the benefit assessment are those that only include documentation up to just before administration of the second dose.

Analyses under treatment are not suitable for the benefit assessment

In the SUPERNOVA study, analyses of events that occurred during treatment were primarily planned for outcomes in the morbidity category (while-on-treatment strategy). Censoring was performed for individuals who experienced one of the following events: unblinding, administration of an additional drug for COVID-19 prophylaxis, and, if applicable, COVID-19 events with virus variants with F456L mutation or missing sequencing results for the virus variant (only for separate analysis for individual virus variants). The analysis on outcomes in the morbidity category primarily described as relevant by the company in Module 4 A of the dossier and prepared according to the dossier template [23] corresponds to this analysis strategy. Analyses in which no censoring was performed in case of the events listed above (treatment policy strategy) were also prespecified as sensitivity analyses in the SUPERNOVA study. However, the company only presented these in Appendix 4 G to Module 4 A of the dossier and did not prepare the data according to the dossier template. This approach is not appropriate. Analyses of the SUPERNOVA study according to the treatment policy strategy are generally relevant for the benefit assessment.

Analyses of adverse events and severe adverse events (CTCAE grade ≥ 3) not suitable

The company presented analyses for the first dose and for the entire observation period of the SUPERNOVA study for outcomes in the side effects category in Module 4 A of the dossier. Analyses of the first dose covered the period from administration of the first dose of study medication to 1 day before administration of the second dose (Day 180) or to Day 188 if no

second dose of study medication was administered. Analyses of the entire observation period included events up to and including the end of the study or the point of data cut-off. However, in the SUPERNOVA study, adverse events (AEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) were only fully monitored up to 90 days after administration of the study medication. Thereafter, only those AEs and severe AEs that were associated with COVID-19 or the study medication in the investigator's opinion were selectively recorded. Only analyses for AEs and severe AEs based on a complete survey of all AEs, i.e. analyses up to Day 91 after administration of the study medication, are suitable for the benefit assessment. For serious AEs, on the other hand, a complete survey was conducted over the entire study period, which is why for this outcome for the first administration of the study medication analyses up to day 180 would also be useful.

Analyses of the outcome of confirmed symptomatic COVID-19

In Module 4 A, the company presented analyses on the outcome confirmed symptomatic COVID-19, both independently of the underlying SARS-CoV-2 variant and separately for virus variants that do not carry an F456L mutation in the spike protein. Analyses independent of the underlying virus variant are generally considered relevant. However, this results in uncertainties regarding the transferability of the results to the current health care context, as it is assumed that the majority of currently circulating SARS-CoV-2 variants carry an F456L mutation (see Chapter I 2). In addition to analyses independent of the underlying SARS-CoV-2 variant, analyses divided by SARS-CoV-2 variants (with or without F456L mutation) would therefore be desirable.

Evidence presented by the company – NOVELLA study

The NOVELLA study is a double-blind RCT comparing sipavibart with placebo for COVID-19 pre-exposure prophylaxis in adults with diseases or co-morbidities that can lead to an impaired immune response after vaccination and who are therefore at high risk of progressing to severe COVID-19. A possible impairment of the immune response should be shown by at least one of the following risk factors in the study participants: obesity (body mass index [BMI] ≥ 30), heart failure, chronic obstructive pulmonary disease, chronic kidney disease (glomerular filtration rate < 30 mL/min/1.73 m^2), intolerance to the vaccine or immunocompromised state.

The study was only conducted in Russian study centres. A total of 116 adults were randomly assigned in a 3:1 ratio to treatment with sipavibart (N = 87) or placebo (N = 29). Treatment was administered intramuscularly with one single dose of the respective study medication, whereby sipavibart was used in accordance with the SPC [4].

The primary outcomes of the NOVELLA study were outcomes in the side effects category. Patient-relevant secondary outcomes were outcomes on morbidity.

In Appendix 4 G to Module 4 A of the dossier, the company presented analyses of the NOVELLA study for a subpopulation with a therapeutic indication for COVID-19 pre-exposure prophylaxis, comprising 15 people in the intervention arm and 11 people in the comparator arm. The formation of this subpopulation was essentially analogous to the previously described procedure used by the company for the SUPERNOVA study.

Concurring with the company, the NOVELLA study is not relevant for the benefit assessment

The NOVELLA study is unsuitable for this benefit assessment. This is in particular due to the fact that the NOVELLA study was conducted in a different health care context. The study was conducted exclusively at study centres in Russia and thus under COVID-19 regulations in this health care context. This had a particular impact on the immunization status of the adults included. Only about half of the individuals in the subpopulation presented by the company were vaccinated against SARS-CoV-2 before the start of the study (9 people [60%] in the intervention arm, 5 people [45%] in the comparator arm). Apart from one person in the comparator arm, for whom no information was available, the Sputnik V/Sputnik Light vaccine was used, which is not approved in the European Union. For those individuals who were not vaccinated against SARS-CoV-2 before the start of the study, no information was available as to why this was the case. For these people, it is therefore unclear whether they were eligible for pre-exposure prophylaxis in accordance with §2 of the COVID-19 Prevention Ordinance. Confirmed previous COVID-19 infections were also only present in some of the individuals in the subpopulation presented by the company (65%), whereby there were only 2 people with 2 infections each in the intervention arm and those affected in the comparator arm had no more than one infection. It therefore cannot be assumed that the adults included in the study had developed basic immunity in accordance with the STIKO recommendations.

As already described, in the German health care context the STIKO recommends that independent of the use of drugs for pre-exposure prophylaxis, people with immunodeficiency should first build up a basic immunity (consisting of at least 3 contacts with the pathogen, at least one of which should be a vaccination), and that they receive annual booster vaccinations against SARS-CoV-2 [22]. The vaccines recommended in this context also differ from the vaccines used in the NOVELLA study. Against the background of these fundamental differences, it is not assumed that the study provides informative data for the German health care context. The company’s approach of not utilizing the NOVELLA study for its assessment is therefore considered appropriate.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of sipavibart in comparison with watchful waiting as the ACT for pre-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments. There is no hint of an added benefit of sipavibart in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of sipavibart in comparison with the ACT is summarized in Table 5.

Table 5: Sipavibart – 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 12 years of age and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments[b, c, d, e, f]	Watchful waiting	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In this therapeutic indication, sipavibart should be used according to official recommendations, if available, and based on information on the activity of sipavibart against currently circulating virus variants.
c. According to §2 of the COVID-19 Prevention Ordinance, entitlement to the provision of prescription drugs for pre-exposure prophylaxis of COVID-19 at the expense of the SHI only exists for insured persons if, for medical reasons, no or no sufficient immune protection against COVID-19 can be achieved by vaccination, or if vaccinations against SARS-CoV-2 coronavirus cannot be carried out due to a contraindication, and they are thus exposed to an increased risk of progressing to severe COVID-19. Medical reasons may include, in particular, congenital or acquired immunodeficiencies, underlying diseases or a relevant impairment of the immune response due to immunosuppressive therapy.
d. It is assumed that study participants in all study arms observe the generally recognized hygiene rules (e.g. social distancing, general hygiene measures) to reduce the risk of infection.
e. 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.
f. 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; VOC: variant of concern

The assessment described above deviates from that of the company, which, on the basis of the analyses of the SUPERNOVA study it provided, derived an indication of considerable added benefit.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-28.html.