Sipavibart
(pre-exposure prophylaxis of COVID 19)

Addendum to Project A25-28
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
COVID-19	coronavirus disease 2019
CSR	clinical study report
CSZ	convexity, symmetry, z-score
CTCAE	Common Terminology Criteria for Adverse-Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SpO_2	oxygen saturation
STIKO	Standing Committee on Vaccination
WHO	World Health Organization

1 Background

On 24 June 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-28 (Sipavibart – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the following information and analyses on the SUPERNOVA study submitted by the company in the commenting procedure [2-4], taking into account the information in the dossier [5]:

- Comparison of sipavibart with placebo
- Data on vaccination status prior to study inclusion and information on previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections
- Results according to treatment policy strategy after dossier submission
- Safety data up to Day 103 after the start of the study, analogue to the study report
- Severe adverse events (AEs) according to System Organ Class (SOC) and Preferred Term (PT)

The responsibility for this 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

For the assessment of the added benefit of sipavibart for the 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 G-BA defined watchful waiting as the appropriate comparator therapy (ACT). However, in its dossier [5], the company presented analyses for the SUPERNOVA study for a subpopulation of study participants with a therapeutic indication for COVID-19 pre-exposure prophylaxis who received either tixagevimab/cilgavimab or placebo in the comparator arm.

The SUPERNOVA study is a randomized controlled trial (RCT) comparing sipavibart with tixagevimab/cilgavimab or placebo. At the beginning of the study, the study participants in the control group were initially treated with tixagevimab/cilgavimab in accordance with the study plan. 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 study medication in the comparator arm of the study; and people who were included after this amendment received placebo. As explained in dossier assessment A25-28 [1], the administration of tixagevimab/cilgavimab in the comparator arm of the SUPERNOVA study does not correspond to the ACT of watchful waiting defined by the G-BA.

In its comments and following the oral hearing [2-4], the company presented analyses for the SUPERNOVA study on the subpopulation of participants with a therapeutic indication for COVID-19 pre-exposure prophylaxis to compare sipavibart with placebo. These data were used for the benefit assessment.

2.1 Studies included

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

Table 1: Study pool – RCT, direct comparison: sipavibart vs. watchful waiting

Study	Study category			Available sources		
	Study for the marketing authorization 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 (yes/no [citation])
SUPERNOVA	Yes	Yes	No	Yes [6]	Yes [7-9]	Yes [10]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.

CSR: clinical study report; RCT: randomized controlled trial

The SUPERNOVA study was used for the benefit assessment. The study pool was consistent with that selected by the company. For the present benefit assessment, analyses for a subpopulation of study participants with a therapeutic indication for COVID-19 pre-exposure prophylaxis who received placebo in the comparator arm are relevant. Deviating from this, in its assessment the company used analyses of a subpopulation that included study participants in the comparator arm who received either tixagevimab/cilgavimab or placebo.

2.2 Study characteristics

Detailed characteristics of the SUPERNOVA study can be found in dossier assessment A25-28 [1].

Relevant subpopulation for the benefit assessment

As explained in the dossier assessment, the company's procedure for identifying study participants with a therapeutic indication for COVID-19 pre-exposure prophylaxis was appropriate. According to the company, the analyses on the comparison of sipavibart with placebo subsequently submitted in the commenting procedure included data on study participants with a therapeutic indication for COVID-19 pre-exposure prophylaxis who were randomized at the respective study centre after implementation of Amendment 6 to the protocol, i.e. after 14 June 2023 at the earliest. The company stated that the centre-specific time point corresponded to the last day at the respective study centre on which the drug combination tixagevimab/cilgavimab was administered in the control arm. If the drug combination tixagevimab/cilgavimab was never used at a centre, this date was set to 14 June 2023, according to the company. The company’s approach was appropriate. The subpopulation resulting from the criteria described above for the comparison of sipavibart with placebo comprised 221 people in the intervention arm and 168 people in the control arm.

Patient characteristics

Table 2 shows the patient characteristics of the subpopulation of the included study.

Table 2: Characteristics of the relevant subpopulation and study/treatment discontinuation – RCT, direct comparison: sipavibart vs. placebo (multipage table)

Study **Characteristic** **Category**	**Sipavibart** **N[a] = 221**	**Placebo** **N[a] = 168**
SUPERNOVA		
Age [years], mean (SD)	58 (13)	57 (12)
≥ 12 to < 18 years, n (%)	0 (0)[b]	0 (0)[b]
≥ 18 to < 65 years, n (%)	150 (68)	118 (70)
≥ 65 years, n (%)	71 (32)	50 (30)
Sex [F/M], %	61/39	51/49
Region, n (%)		
United States	165 (75)	119 (71)
Europe	42 (19)	44 (26)
Rest of the world	14 (6)	5 (3)
BMI [kg/m^2], mean (SD)	29.4 (7.3)	28.7 (7.4)
SARS-CoV-2 PCR status, n (%)		
Not determined	195 (88)	156 (93)
No usable result	2 (< 1)	0 (0)
Missing	24 (11)	12 (7)
SARS-CoV-2 infection in the past[c], n (%)		
Yes	99 (45)[b]	75 (45)[b]
No	122 (55)[b]	93 (55)[b]
SARS-CoV-2 infection within the 6 months before randomization, n (%)		
Yes	3 (1)	2 (1)
No	218 (99)	166 (99)
COVID-19 vaccination within the 6 months before randomization, n (%)		
Yes	26 (12)	19 (11)
No	195 (88)	149 (89)

Table 2: Characteristics of the relevant subpopulation and study/treatment discontinuation – RCT, direct comparison: sipavibart vs. placebo (multipage table)

Study **Characteristic** **Category**	**Sipavibart** **N[a] = 221**	**Placebo** **N[a] = 168**
Last COVID-19 vaccination administered[d]		
No vaccination documented	118 (53)	89 (53)
First dose	3 (1)	5 (3)
Second dose	13 (6)	12 (7)
Third dose	30 (14)	21 (13)
Fourth dose	20 (9)	15 (9)
Fifth dose	22 (10)	20 (12)
> fifth dose	15 (7)	6 (4)
Treatment discontinuation, n (%)	–[e]	–[e]
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients at baseline without a positive SARS-CoV-2 RT-PCR test result who received at least 1 dose of the respective treatment.
b. Institute's calculation.
c. It is assumed that this relates to information on SARS-CoV-2 infections in the past without restriction to a period prior to randomization or study inclusion.
d. It is assumed that this relates to information on the last COVID-19 vaccination dose generally received, without restriction to a period before randomization or the start of the study.
e. No suitable data; see Section 2.3 for reasons.

F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation

The demographic and clinical characteristics of the study participants in both treatment arms were largely comparable. At baseline the participants in the intervention arm were on average 58 years old, in the control arm 57 years old, with around 1 third of the people in each study arm being older than 65 years. No person was younger than 18. There were slightly more women in the intervention arm (61%) than in the control arm (51%). The majority of the study participants came from the United States and Europe, and the average body mass index was around 29.

In both study arms, 45% of participants had already had a SARS-CoV-2 infection in the past. Only 1% of study participants had a SARS-CoV-2 infection within the 6 months prior to randomization, while just over 10% of study participants received a vaccination against COVID-19 during this period. Vaccination was not documented for around half of the study participants. It is not possible to tell from this information whether these people were unvaccinated or whether the information on vaccination status was not documented. For the

majority of people with documented vaccination, the last COVID-19 vaccination received was at least the third vaccination dose.

The company's information on discontinuation of therapy only included immediate hypersensitivity reactions after administration of the first dose of the study medication that led to the second dose of the study medication not being administered. These data were not suitable for the benefit assessment (see Section 2.3 for justification). Data on the proportion of people who discontinued the study were not available for the placebo comparison. In the overall study population, 2 people in the intervention arm and 1 person in the control arm (tixagevimab/cilgavimab or placebo) had discontinued the study due to AEs by the data cut-off.

Limitations of the study

As described in dossier assessment A25-28, full immunization against COVID-19 is also recommended for people with a relevant risk of an inadequate vaccination response [1]. However, since there was no documentation of COVID-19 vaccinations for half of the study participants in the placebo comparison, it is not possible to estimate whether full immunization can be assumed for the population under consideration as a whole. It therefore remains unclear whether the observed effects are directly transferable to a fully immunized group of people. Since it is also unclear how high the proportion of people with full immunization is in the German health care context, this aspect had no consequences for the benefit assessment.

According to the inclusion criteria, adolescents aged 12 and over as well as adults were eligible to participate in the SUPERNOVA study. However, the relevant subpopulation did not include people in the age group ≥ 12 years to < 18 years. Therefore, no conclusions could be drawn from the available data for this age group.

Risk of bias across outcomes (study level)

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: Risk of bias across outcomes (study level) – RCT, direct comparison: sipavibart vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
SUPERNOVA	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the SUPERNOVA study.

Transferability of the study results to the German health care context

The company presumed the SUPERNOVA study results to be generally transferable to the German health care context. It justified this in particular by the fact that the population presented with a therapeutic indication for COVID-19 pre-exposure prophylaxis was defined according to the criteria of the German COVID-19 Prevention Ordinance and the German Standing Committee on Vaccination (STIKO) for pre-exposure prophylaxis of COVID-19, and thus represents the German health care context. In addition, the company stated that participants for the SUPERNOVA study were recruited not only in Germany but also in countries where the health care context was largely comparable to Germany in terms of the SARS-CoV-2 vaccines used in everyday practice and the goal of achieving basic immunization through vaccination. Furthermore, the company argued that although information on vaccination status was missing for half of the population presented, data on a comparable population in Germany is currently not available. According to the company, existing data for a general risk population for severe progression of COVID-19 indicate a rather low vaccination rate compared to the current STIKO recommendations. It stated that the SUPERNOVA study design, the locations of the study centres and the participant data with available information on vaccination status did not result in any evidence to suggest lower baseline immunity and fewer annual booster vaccinations in the subpopulation compared to the German health care context. The company maintained that in any case, a strong reduction in the vaccination response can be assumed for people with a therapeutic indication for COVID-19 pre-exposure prophylaxis, so that transferability to the German health care context can be assumed. Furthermore, the company stated that the mean age of the study population was only marginally below the average age of people with an inadequate response to active immunization against COVID-19 in Germany as determined by a routine data analysis of statutory health insurance companies. Finally, according to the company, the factors age, sex,

region, family origin and the presence of certain risk factors did not result in any effect modifications relevant to the conclusion.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also the section above regarding limitations of the study.

2.3 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Confirmed symptomatic COVID-19
  - Severe COVID-19
- Health-related quality of life
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviates from those of the company, which used further outcomes in the dossier (Module 4 A) and in its comments.

Table 4 shows for which outcomes data were available in the included study.

Table 4: Matrix of outcomes – RCT, direct comparison: sipavibart vs. placebo

Study	Outcomes							
	All-cause mortality[a]	Confirmed symptomatic COVID-19	Severe COVID-19[b]	Health-related quality of life	SAEs[c]	Severe AEs[c, d]	Discontinuation due to AEs	Specific AEs
SUPERNOVA	Yes	Yes	Yes	No[e]	Yes	Yes	–[f]	No[g]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Severe COVID-19 was defined as a combination of a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 [11] and the presence of at least 1 of the following 2 events: pneumonia (fever ≥ 38°C, cough, tachypnoea or dyspnoea and pulmonary infiltrates) or hypoxaemia (SpO_2 < 90% on room air and/or severe dyspnoea).
c. Overall rate excluding events classified by the company as late complications of COVID-19; see body of text below for reasons.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Outcome not recorded.
f. No suitable data, see body of text below for reasons.
g. No specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; SpO_2: blood oxygen saturation; WHO: World Health Organization

Notes on analysis periods and outcomes

Relevant analysis period

In the SUPERNOVA study, 2 treatments (Day 1 and Day 181) with the study medication were planned. The 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. During the course of the study, the administration of a second dose of the respective study medication was additionally scheduled for Day 181. As described in dossier assessment A25-28, the company presented analyses for study participants with a therapeutic indication for COVID-19 pre-exposure prophylaxis. The criteria for the therapeutic indication for pre-exposure prophylaxis were based on patient characteristics at baseline. In its comments, the company also 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. Consequently, only analyses that only included recordings up to immediately before administration of the second dose (Day 181) were relevant for the benefit assessment.

Morbidity

For the outcomes on morbidity, the company presented analyses up to Day 91 and up to Day 181. The analyses up to Day 181 were used for the benefit assessment, as these represented the longest observation period before potential administration of the second dose of sipavibart or placebo (see above). Analyses up to Day 91 are presented in Appendix A.

Furthermore, the company presented analyses of SARS-CoV-2 infections with any virus variant as well as infections without F456L mutation for the outcomes on morbidity. Those for any virus variants were used for the benefit assessment. Analyses of infections without an F456L mutation are presented as supplementary information in Appendix A in Table 11. The company did not present analyses on infections with F456L mutation.

Confirmed symptomatic COVID-19

Confirmed symptomatic COVID-19 was defined in the SUPERNOVA study as the presence of a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test in those participants who had a negative SARS-CoV-2 RT-PCR test at baseline, with symptoms present at the same time. This was operationalized based on the World Health Organization (WHO) COVID-19 case definitions [12] and included the following clinical criteria:

- Two of the following criteria: Acute onset of fever, cough, positive COVID-19 test (rapid antigen test or RT-PCR)

or

- Acute occurrence of 3 or more of the following criteria: fever, cough, general weakness/tiredness, headache, myalgia, sore throat, rhinitis, dyspnoea, nausea/diarrhoea/anorexia, conjunctivitis, positive COVID-19 test, symptom associated with COVID-19 according to investigator assessment.

In order to determine the incidence of COVID-19, the study participants were contacted weekly by the centres in the first year, and monthly thereafter.

The definition of confirmed symptomatic COVID-19 was adequate and the outcome was used for the benefit assessment.

Severe COVID-19

Severe COVID-19 was defined in the SUPERNOVA study as a combination of a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 [11] and the presence of at least one of the

following 2 events: pneumonia (fever ≥ 38°C, cough, tachypnoea or dyspnoea and pulmonary infiltrates) or hypoxaemia (blood oxygen saturation [SpO_2] < 90% on room air and/or severe dyspnoea).

These events are suitable for adequately representing severe progression of COVID-19, as they concur with severe symptoms. A WHO score of 5 or higher also means that those affected are hospitalized and require oxygen. The outcome was therefore used in the benefit assessment.

Side effects

For outcomes in the side effects category, the company presented overall rates both including and excluding events that it assessed as late complications of COVID-19. The company's list of these events (see appendix 4 G of the dossier [5]) included numerous events that essentially reflect the symptoms of COVID-19. However, it is difficult to differentiate between symptoms caused by COVID-19 and adverse events. For example, the company excluded headaches as a COVID-19-related symptom from its analysis, but headaches can also occur independently of a COVID-19 infection. Since the overall rates including and excluding the events assessed as late complications were comparable and it could be excluded with sufficient certainty that neither advantages nor disadvantages in these outcomes were overlooked (see Table 6), this had no consequences for the benefit assessment. For this addendum, the overall rates excluding potentially COVID-19-related events were used.

In addition to analyses for SAEs and severe AEs, the company presented results on the outcome discontinuation due to AEs. According to the study protocol, immediate hypersensitivity reactions following administration of the first dose of the study medication that resulted in the second dose of the study medication not being administered were recorded under discontinuation of the study medication. This definition is not suitable to reflect the outcome of discontinuation due to AEs for the benefit assessment, as it does not cover all AEs that may lead to discontinuation of therapy before the second dose of the study medication is administered. No suitable data were therefore available for the benefit assessment for the outcome of discontinuation due to AEs.

SAEs

In the SUPERNOVA study, SAEs were observed over the entire study period. Analyses were planned up to Day 91 and over the entire study period. In its comments, the company presented analyses on the outcome SAEs up to Day 91, Day 181 and over the entire observation period up to the data cut-off on 29 March 2024 (including recordings after administration of the second dose of the study medication). Analyses up to Day 181 were used for this addendum, as only analyses that only included recordings prior to administration of the second dose of study medication were relevant (see above).

Severe AEs

In the SUPERNOVA study, severe AEs were operationalized as CTCAE grade ≥ 3. The recording of AEs and severe AEs was complete in the SUPERNOVA study for 90 days after administration of the study medication. In the subsequent period between Day 91 and the administration of the second dose of the study medication on Day 181, only those AEs were recorded that were related to COVID-19 or the study medication according to the investigator's assessment. The company presented analyses for the placebo comparison for the outcome severe AEs up to Day 91, Day 181 as well as over the entire observation period up to the data cut-off on 29 March 2024 (including recordings after administration of the second dose of the study medication). The selective recording of AEs between Day 91 and the administration of the second dose of the study medication, as well as analyses that included events from the administration of the second dose of the study medication onwards, were not relevant for the benefit assessment. Therefore, analyses up to Day 91 were used for the outcome severe AEs in this addendum.

2.4 Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: sipavibart vs. placebo

Study	Study level	Outcomes							
		All-cause mortality[a]	Confirmed symptomatic COVID-19	Severe COVID-19[b]	Health-related quality of life	SAEs[c]	Severe AEs[c, d]	Discontinuation due to AEs	Specific AEs
SUPERNOVA	L	L	L	L	–[e]	L	L	–[f]	–[g]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Severe COVID-19 was defined as a combination of a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 [11] and the presence of at least 1 of the following 2 events: pneumonia (fever ≥ 38 °C, cough, tachypnoea or dyspnoea and pulmonary infiltrates) or hypoxaemia (SpO_2 < 90% on room air and/or severe dyspnoea).
c. Overall rate excluding events classified by the company as late complications of COVID-19; see Section 2.3 for reasons.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Outcome not recorded.
f. No suitable data; see Section 2.3 for reasons.
g. No specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; COVID-19: coronavirus disease 2019; CTCAE: Common Terminology Criteria for Adverse Events; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SpO_2: blood oxygen saturation; WHO: World Health Organization

The risk of bias for the results on all outcomes for which usable data were available was rated as low.

2.5 Results

Table 6 summarizes the results for the comparison of sipavibart with placebo 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. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's comments.

Tables on common AEs, SAEs and severe AEs are presented in Appendix B.

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sipavibart vs. placebo (multipage table)

Study Outcome category Outcome Time point	Sipavibart N	Sipavibart Individuals with event n (%)	Placebo N	Placebo Individuals with event n (%)	Sipavibart vs. placebo RR [95% CI]; p-value[a]
SUPERNOVA					
Mortality					
All-cause mortality[b] up to Day 181	221	1 (0.5)	168	1 (0.6)	0.76 [0.05; 12.07]; 0.912
Morbidity					
Confirmed symptomatic COVID-19 (any SARS-CoV-2 variant)					
Up to Day 181	221	21 (9.5)	168	22 (13.1)	0.68 [0.37; 1.25]; 0.216
Severe COVID-19[c] (any SARS-CoV-2 variant)					
Up to Day 181	221	0 (0)	168	0 (0)	–
Health-related quality of life	Outcome not recorded				
Side effects[d]					
AEs up to Day 91[e] (shown additionally)	221	133 (60.2)	168	94 (56.0)	–
SAEs[f] up to Day 181[g]	221	25 (11.3)	168	17 (10.1)	1.12 [0.62; 2.00]; 0.725
Severe AEs[h, i] up to Day 91[e]	221	20 (9.0)	168	11 (6.5)	1.38 [0.68; 2.81]; 0.377
Discontinuation due to AEs	No suitable data[j]				

Table 6: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: sipavibart vs. placebo (multipage table)

Study	Sipavibart		Placebo		Sipavibart vs. placebo
Outcome category Outcome Time point	N	Individuals with event n (%)	N	Individuals with event n (%)	RR [95% CI]; p-value[a]

a. Morbidity outcomes, RR, CI and p-value: Poisson model with robust variance, with the stratification factors COVID-19 vaccination within 6 months before randomization (yes vs. no), administration of tixagevimab/cilgavimab within 12 months before randomization (yes vs. no) and SARS-CoV-2 infection within 6 months before randomization (yes vs. no) as covariates and the logarithmic follow-up time as offset; mortality and side effects outcomes: estimation is unstratified, CI calculation asymptotic, p-value from Institute's calculation (unconditional exact test [CSZ method according to [13]).
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Severe COVID-19 was defined as a combination of a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 and the presence of at least 1 of the following 2 events: pneumonia (fever ≥ 38°C, cough, tachypnoea or dyspnoea and pulmonary infiltrates) or hypoxaemia (SpO_2 < 90% on room air and/or severe dyspnoea).
d. Excluding events that were rated by the company as late complications of COVID-19
e. According to the company, events that occurred within a follow-up period of 90 days after administration of the study medication plus a tolerance window of 13 days were taken into account.
f. SAEs including events that were rated by the company as late complications of COVID-19, n (%) sipavibart vs. placebo: 25 (11.3 %) vs. 21 (12.5 %), RR [95% CI]; p-value (unconditional exact test [CSZ method according to [13]): 0.90 [0.53; 1.56]; 0.730
g. Or up to Day 188 if no second dose of study medication was administered
h. Operationalized as CTCAE grade ≥ 3.
i. Severe AEs including events that were rated by the company as late complications of COVID-19, n (%) sipavibart vs. placebo: 20 (9.0 %) vs. 14 (8.3 %), RR [95% CI]; p-value (unconditional exact test [CSZ method according to [13]): 1.09 [0.57; 2.09]; 0.844
j. See Section 2.3 for reasons.

AE: adverse event; CI: confidence interval; COVID-19: coronavirus disease 2019; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: blood oxygen saturation; WHO: World Health Organization

Based on the available information, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

The results on all-cause mortality were based on data on fatal AEs.

No statistically significant difference between treatment groups was found for the outcome of all-cause mortality. There is no hint of an added benefit of sipavibart in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Confirmed symptomatic COVID-19 (any SARS-CoV-2 variant) and severe COVID-19 (any SARS-CoV-2 variant)

For the outcomes confirmed symptomatic COVID-19 (any SARS-CoV-2 variant) and severe COVID-19 (any SARS-CoV-2 variant), there was no statistically significant difference between the treatment groups. In each case there is no hint of an added benefit of sipavibart in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

The outcome health-related quality of life was not recorded in the SUPERNOVA study.

Side effects

SAEs and severe AEs

No statistically significant difference between the treatment groups was shown for the outcomes SAEs (up to Day 181) and severe AEs (up to Day 91). In each case, there is no hint of greater or lesser harm of sipavibart in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No suitable data were available for the outcome of discontinuation due to AEs (see Section 2.3 for reasons). There is no hint of greater or lesser harm from sipavibart in comparison with watchful waiting; greater or lesser harm is therefore not proven.

2.6 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this benefit assessment:

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

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

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

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

2.7 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [14].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.7.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.5 (see Table 7).

Table 7: Extent of added benefit at outcome level: sipavibart vs. watchful waiting

Outcome category **Outcome**	**Sipavibart vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.5% vs. 0.6% RR: 0.76 [0.05; 12.07]; p = 0.912	Lesser benefit/added benefit not proven
Morbidity		
Confirmed symptomatic COVID-19 (any SARS-CoV-2 variant)	9.5% vs. 13.1% RR: 0.68 [0.37; 1.25]; p = 0.216	Lesser benefit/added benefit not proven
Severe COVID-19 (any SARS-CoV-2 variant)	0 % vs. 0 %	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	11.3 % vs. 10.1 % RR: 1.12 [0.62; 2.00]; p = 0.725	Greater/lesser harm not proven
Severe AEs	9.0 % vs. 6.5 % RR: 1.38 [0.68; 2.81]; p = 0.377	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COVID-19: corona virus disease 2019; RR: relative risk; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

2.7.2 Overall conclusion on added benefit

Table 8 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of sipavibart in comparison with watchful waiting

Positive effects	**Negative effects**
–	–
No data were available on health-related quality of life or discontinuation due to AEs.	
AE: adverse event	

Overall, there are neither positive nor negative effects for sipavibart in comparison with placebo for pre-exposure prophylaxis of COVID-19 in adults who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments. Data on health-related quality of life and suitable data on the outcome discontinuation due to AEs were not available.

No data were available for 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.

In summary, there is no added benefit of sipavibart versus the ACT of watchful waiting for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and who are immunocompromised due to a medical condition or receipt of immunosuppressive treatments.

2.8 Summary

The data subsequently submitted by the company in the commenting procedure do not change the conclusion on the added benefit of sipavibart drawn in dossier assessment A25-28 [1].

The following Table 9 shows the result of the benefit assessment of sipavibart under consideration of dossier assessment A25-28 and the present addendum.

Table 9: 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.

3 References

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Appendix A Results from the SUPERNOVA study presented as supplementary information

Morbidity results – any SARS-CoV-2 variant up to Day 91

Table 10: Results (morbidity up to Day 91, any SARS-CoV-2 variant, supplementary presentation) – RCT, direct comparison: sipavibart vs placebo

Study	Sipavibart		Placebo		Sipavibart vs. placebo
Outcome category Outcome Time point	N	Individuals with event n (%)	N	Individuals with event n (%)	RR [95% CI]; p-value[a]
SUPERNOVA					
Morbidity					
Confirmed symptomatic COVID-19 (any SARS-CoV-2 variant)					
Up to Day 91	221	14 (6.3)	168	19 (11.3)	0.55 [0.27; 1.09]; 0.087
Severe COVID-19[b] (any SARS-CoV-2 variant)					
Up to Day 91	221	0 (0)	168	0 (0)	–

a. RR, CI and p-value: Poisson model with robust variance, with the stratification factors COVID-19 vaccination within 6 months before randomization (yes vs. no), administration of tixagevimab/cilgavimab within 12 months before randomization (yes vs. no) and SARS-CoV-2 infection within 6 months before randomization (yes vs. no) as covariates and the logarithmic follow-up time as offset.

b. Severe COVID-19 was defined as a combination of a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 and the presence of at least 1 of the following 2 events: pneumonia (fever ≥ 38°C, cough, tachypnoea or dyspnoea and pulmonary infiltrates) or hypoxaemia (SpO_2 < 90% on room air and/or severe dyspnoea).

CI: confidence interval; COVID-19: coronavirus disease 2019; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: blood oxygen saturation; WHO: World Health Organization

Morbidity results – SARS-CoV-2 variants without F456L mutation

Table 11: Results (morbidity, SARS-CoV-2 variants without F456L mutation, supplementary presentation) – RCT, direct comparison: sipavibart vs placebo

Study	Sipavibart		Placebo		Sipavibart vs. placebo
Outcome category Outcome Time point	N	Individuals with event n (%)	N	Individuals with event n (%)	RR [95% CI]; p-value[a]
SUPERNOVA					
Morbidity					
Confirmed symptomatic COVID-19 (SARS-CoV-2 variants without F456L mutation)					
Up to Day 91	221	4 (1.8)	168	8 (4.8)	0.37 [0.11; 1.24]; 0.107
Up to Day 181	221	10 (4.5)	168	10 (6.0)	0.73 [0.30; 1.75]; 0.481
Severe COVID-19[b] (SARS-CoV-2 variants without F456L mutation)					
Up to Day 91	221	0 (0)	168	0 (0)	–
Up to Day 181	221	0 (0)	168	0 (0)	–

a. RR, CI and p-value: Poisson model with robust variance, with the stratification factors COVID-19 vaccination within 6 months before randomization (yes vs. no), administration of tixagevimab/cilgavimab within 12 months before randomization (yes vs. no) and SARS-CoV-2 infection within 6 months before randomization (yes vs. no) as covariates and the logarithmic follow-up time as offset.

b. Severe COVID-19 was defined as a combination of a score ≥ 5 on the WHO Clinical Progression Scale for COVID-19 and the presence of at least 1 of the following 2 events: pneumonia (fever ≥ 38 °C, cough, tachypnoea or dyspnoea and pulmonary infiltrates) or hypoxaemia (SpO_2 < 90% on room air and/or severe dyspnoea).

CI: confidence interval; COVID-19: coronavirus disease 2019; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: blood oxygen saturation; WHO: World Health Organization

Appendix B Results on side effects

For the overall rates of AEs, SAEs and severe AEs (CTCAE grade ≥ 3), the following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5 % of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

Table 12: Common AEs[a, b] up to Day 91[c] – RCT, direct comparison: sipavibart vs placebo

Study	Patients with event n (%)	
SOC[d] **PT[d]**	**Sipavibart** **N = 221**	**Placebo** **N = 168**
SUPERNOVA		
Overall AE rate[b]	144 (65.2)	100 (59.5)
Blood and lymphatic system disorders	12 (5.4)	1 (0.6)
Gastrointestinal disorders	24 (10.9)	17 (10.1)
Diarrhoea	11 (5.0)	9 (5.4)
General disorders and administration site conditions	36 (16.3)	31 (18.5)
Fatigue	11 (5.0)	11 (6.5)
Infections and infestations	76 (34.4)	50 (29.8)
COVID-19	14 (6.3)	22 (13.1)
Upper respiratory tract infection	16 (7.2)	7 (4.2)
Urinary tract infection	14 (6.3)	3 (1.8)
Injury, poisoning and procedural complications	15 (6.8)	8 (4.8)
Metabolism and nutrition disorders	14 (6.3)	8 (4.8)
Musculoskeletal and connective tissue disorders	17 (7.7)	19 (11.3)
Myalgia	6 (2.7)	10 (6.0)
Nervous system disorders	18 (8.1)	21 (12.5)
Headache	9 (4.1)	13 (7.7)
Respiratory, thoracic and mediastinal disorders	40 (18.1)	27 (16.1)
Cough	13 (5.9)	14 (8.3)
Nasal congestion	11 (5.0)	7 (4.2)
Oropharyngeal pain	13 (5.9)	7 (4.2)
Vascular disorders	10 (4.5)	6 (3.6)

a. Events that occurred in at least one study arm in ≥ 10% of patients.
b. Including events that were rated by the company as late complications of COVID-19.
c. According to the company, events that occurred within a follow-up period of 90 days after administration of the study medication plus a tolerance window of 13 days were taken into account.
d. No information on the MedDRA version used; SOC and PT spelling taken from the comments without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Common SAEs[a, b] up to Day 181[c] – RCT, direct comparison: sipavibart vs placebo

Study	Patients with event n (%)	
SOC[d]	**Sipavibart N = 221**	**Placebo N = 168**
SUPERNOVA		
Overall rate of SAEs[b, e]	25 (11.3)	21 (12.5)
Infections and infestations	10 (4.5)	10 (6.0)

a. Events that occurred in ≥ 5 % of the patients in at least one study arm.
b. Including events that were rated by the company as late complications of COVID-19.
c. Or up to Day 188 if no second dose of study medication was administered.
d. No information on the MedDRA version used; SOC spelling taken from the comments without adaptation.
e. For SAEs, no MedDRA PTs met the criterion for presentation.

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

Table 14: Common severe AEs[a, b] up to Day 91[c] – RCT, direct comparison: sipavibart vs placebo

Study	Patients with event n (%)	
	Sipavibart N = 221	**Placebo N = 168**
SUPERNOVA		
Overall rate of severe AEs[d, e]	20 (9.0)	14 (8.3)

a. Events that occurred in at least one study arm in ≥ 5% of patients.
b. Operationalized as CTCAE grade ≥ 3.
c. According to the company, events that occurred within a follow-up period of 90 days after administration of the study medication plus a tolerance window of 13 days for the visit on Day 91 were taken into account.
d. Including events that were rated by the company as late complications of COVID-19.
e. For severe AEs up to Day 91, no MedDRA SOCs and PTs met the criterion for presentation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class