Risankizumab (Crohn's disease)

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

EXTRACT

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Patient and family involvement

No feedback was received in the framework of the present 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
CDAI	Crohn's Disease Activity Index
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IBDQ	Inflammatory Bowel Disease Questionnaire
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MI	multiple imputation
NRI	non-responder imputation
PRO	patient-reported outcome
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TNF	tumour necrosis factor

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug risankizumab. 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 21 December 2022.

Research question

The aim of this report is to assess the added benefit of risankizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

The research questions shown in Table 2 result from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of risankizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to conventional therapy	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]
2	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-alpha antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or **interleukin inhibitor (ustekinumab)**[c, d]

a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with moderate to severe Crohn's disease who are still eligible for drug therapy (such as biologics) are assumed not to be candidates for surgical resection of affected bowel segments.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose modification options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The company followed the G-BA's specification of the ACT for both research questions. For research question 1, it did not make a selection; for research question 2, it selected ustekinumab as ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Below, research question 2 of the present benefit assessment is addressed first, as the company submitted data for the assessment of the added benefit of risankizumab only for this research question. Research question 1 is then addressed.

Research question 2: patients who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy

Study pool and study design

The SEQUENCE study is used for the benefit assessment. The SEQUENCE study is an ongoing, open-label RCT comparing risankizumab with ustekinumab in adult patients with active moderate to severe Crohn's disease who have had an inadequate response or were intolerant to tumour necrosis factor (TNF)-alpha antagonists. The diagnosis must have been established at least 3 months before enrolment.

Disease severity and activity was defined using the following criteria at study start: Crohn's Disease Activity Index (CDAI) score 220 to 450 at baseline; endoscopic evidence of mucositis documented by a Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥ 6 for ileocolonic or colonic disease, or ≥ 4 for isolated ileal disease, as well as an average daily stool frequency of ≥ 4, and/or an average daily abdominal pain score of ≥ 2 (on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe) at baseline recorded by patient diary. For the present benefit assessment, the severity definition using the inclusion criteria of the SEQUENCE study is deemed a sufficient approximation of moderate to severe Crohn's disease.

In order to participate in the study, patients had to have demonstrated lack of response or intolerance to TNF-alpha antagonists at least 8 weeks before baseline. Other prior therapies such as integrin inhibitors or interleukin inhibitors were not allowed in the SEQUENCE study. Patients with current diagnosis of ulcerative colitis or indeterminate colitis were excluded from the study. Furthermore, patients were not allowed to have any manifestations (e.g. abdominal abscesses, toxic megacolon) that could have required surgery during study participation. Patients who had been treated with corticosteroids for at least 14 days before baseline, with a stable dose for at least 7 days, were eligible to participate in the study.

Patients were randomly allocated to the study arms in a 1:1 ratio. Randomization was stratified by number of previous failed TNF-alpha antagonists (≤ 1, > 1) and baseline corticosteroid use (yes, no). A total of 265 patients were randomized to the risankizumab arm and 262 patients to the ustekinumab arm.

From protocol version 2 onwards, treatment with risankizumab was in compliance with the Summary of Product Characteristics (SPC). Protocol version 1 of the SEQUENCE study dated 23 July 2020 had still specified an induction dosage of 1200 mg, which was not in compliance with the SPC. Protocol version 2 dated 28 September 2021 adjusted the dosage to the currently approved dosage based on the approval granted during the course of the study (see below for the consequences for the analysis population presented). Treatment with ustekinumab was not fully in compliance with the SPC, as the maintenance dose was administered to all patients at an 8-week interval (see below for further details and consequences for the certainty of conclusions).

Initiating corticosteroid therapy or increasing the dose beyond the baseline level as concomitant treatment is in principle not allowed during the study, but this does not necessarily have to lead to discontinuation of the study medication. In these cases, the study medication should only be discontinued if, in the opinion of the investigator, continuation would represent a risk for the study participant.

The duration of treatment is 48 weeks or until the occurrence of unacceptable toxicity or discontinuation of therapy following decision by the physician or patient.

Primary outcomes of the study are clinical remission (CDAI < 150) at week 24 and endoscopic remission at week 48. Furthermore, patient-relevant outcomes on morbidity, health-related quality of life, and side effects are recorded.

Data cut-offs

In Module 4 A, the company presented results for the prespecified data cut-off 1 (interim lock 1) from 13 July 2022. This data cut-off was planned as soon as approximately 50% of the randomized patients had been treated for at least 24 weeks or had discontinued the study prematurely. At the time point of the data cut-off, these were 135 patients in the risankizumab arm and 137 patients in the ustekinumab arm. This data cut-off is used for the benefit assessment. In principle, results at week 24 are considered; however, according to the information provided by the company in Module 4 A, analyses are available for the side effects outcomes (including mortality) that occurred before 22 June 2022, i.e. possibly also beyond week 24.

Analysis population presented by the company

As already described above, the induction dosage of risankizumab was only adjusted to the currently valid approval with protocol version 2. The company therefore presented analyses for a prespecified subpopulation that only included patients in the intervention arm with risankizumab treatment that was in compliance with the SPC (N = 128 in the risankizumab arm, N = 137 in the ustekinumab arm). A total of 7 patients randomized to the risankizumab arm under protocol version 1 were therefore not considered in the analyses presented by the

company. However, the company's approach to only exclude the 7 patients in the intervention arm from the analyses is not appropriate. Although it is comprehensible in principle to exclude from the analyses patients with treatment that is not in compliance with the SPC, in the present case this potentially leads to an imbalance between intervention and comparator arm in relevant baseline characteristics, which were partly used as stratification factors (e.g. treatment with corticosteroids at baseline). Although these were only few patients, this is relevant in the present data situation in addition to other aspects when analysing the efficacy outcomes.

Limitations of the SEQUENCE study

The results of the SEQUENCE study are used for the benefit assessment. However, there are limitations. These uncertainties are described below.

Prior TNF-alpha antagonist therapies

According to the data provided by the company, around 75% of patients had received ≤ 1 previous failed therapy with a TNF-alpha antagonist. Based on these data, it remains unclear whether and, if so, how many patients had not received (documented) previous therapy with a TNF-alpha antagonist (corresponding to < 1). These patients would not be covered by the present therapeutic indication. Due to the clear inclusion criteria regarding necessary prior therapies as well as no recorded protocol violations for this criterion, it is not assumed that this is a relevant proportion of the included patients. The resulting uncertainty is taken into account in the assessment of the certainty of conclusions.

Implementation of the appropriate comparator therapy

The SEQUENCE study used ustekinumab as comparator therapy. In the study, treatment with ustekinumab was induced with a weight-dependent intravenous single dose in compliance with the SPC. 8 weeks after the intravenous induction dose, ustekinumab was administered subcutaneously every 8 weeks at a dose of 90 mg. However, the SPC recommends treatment every 12 weeks after the first subcutaneous administration of 90 mg ustekinumab. Patients who lose response on a treatment every 12 weeks may benefit from increasing the dosage frequency to 8 weeks. Based on the clinical assessment, these patients may then receive the next dose either every 8 weeks or every 12 weeks. In the SEQUENCE study, ustekinumab was therefore not administered fully in compliance with the SPC. It is unclear to what extent this deviation influences the effects of the patient-relevant outcomes observed in the study. This uncertainty is taken into account in the assessment of the certainty of results.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the SEQUENCE study is rated as low. The risk of bias is rated as high for the results of all outcomes except the outcome of all-cause mortality. For the SAEs and severe AEs, it is not clear from the data provided by the company how many of the

patients who discontinued the study per treatment arm were actually followed up after study discontinuation and were therefore included in the analyses. As the proportion of patients who discontinued the study differs between the treatment arms (7% versus 21%), the uncertainty described above is taken into account in the risk of bias. The results for SAEs and severe AEs thus have a high risk of bias. The outcome of discontinuation due to AEs also has a high risk of bias. This is due to lack of blinding in subjective recording of outcomes.

The overall certainty of conclusions of the SEQUENCE study is limited due to the described uncertainties regarding the number of patients who may not be comprised by the present therapeutic indication, and to the fact that the administration of ustekinumab in the control arm was not fully in compliance with the SPC. Irrespective of the low outcome-specific risk of bias in some cases, at most hints, e.g. of added benefit, can therefore be derived on the basis of the available information for all outcomes.

Results

Mortality

All-cause mortality

In the SEQUENCE study, deaths were recorded under adverse events (AEs). No deaths occurred in either treatment arm. There is no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Clinical remission (patient-reported outcomes [PRO]-2), symptoms (Inflammatory Bowel Disease Questionnaire [IBDQ]: bowel symptoms, systemic symptoms)

No suitable data are available for the outcome of clinical remission, recorded with the PRO-2, and the outcome of symptoms, recorded with the IBDQ subscores of bowel symptoms and systemic symptoms. In each case, there is no hint of an added benefit of risankizumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score and SF-36

No suitable data are available for the outcome of health-related quality of life, recorded with the IBDQ total score and the Short Form 36 Health Survey (SF-36). In each case, there is no hint of an added benefit of risankizumab in comparison with ustekinumab; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of serious AEs (SAEs), severe AEs or discontinuation due to AEs. There is no hint of greater or lesser harm from risankizumab in comparison with ustekinumab for any of them; greater or lesser harm is therefore not proven.

Research question 1: patients who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

Results

The company presented no suitable data for the assessment of the added benefit of risankizumab in comparison with the ACT in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy.

Results on added benefit

Because no data are available for the present research question, there is no hint of added benefit of risankizumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

Research question 2: patients who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy

Overall, neither positive nor negative effects were shown for the outcome categories of mortality and side effects. There are no suitable data for the outcome categories of morbidity and health-related quality of life.

[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].

In summary, the added benefit of risankizumab in comparison with the ACT is not proven for adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy.

Research question 1: patients who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

Since the company presented no data for the assessment of the added benefit of risankizumab in comparison with the ACT for adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy, an added benefit of risankizumab is not proven for research question 1.

Table 3 summarizes the probability and extent of added benefit of risankizumab.

Table 3: Risankizumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to conventional therapy	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]	Added benefit not proven
2	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-alpha antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or **interleukin inhibitor (ustekinumab)**[c, d]	Added benefit not proven[e]

a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with moderate to severe Crohn's disease who are still eligible for drug therapy (such as biologics) are assumed not to be candidates for surgical resection of affected bowel segments.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose modification options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.
e. The SEQUENCE study only included patients who had an inadequate response to TNF-alpha antagonists. It remains unclear whether the observed effects can be transferred to patients with previous integrin inhibitor or interleukin inhibitor therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

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

I 2 Research question

The aim of this report is to assess the added benefit of risankizumab in comparison with the ACT in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

The research questions shown in Table 4 result from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of risankizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to conventional therapy	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]
2	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-alpha antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or **interleukin inhibitor (ustekinumab)**[c, d]

a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with moderate to severe Crohn's disease who are still eligible for drug therapy (such as biologics) are assumed not to be candidates for surgical resection of affected bowel segments.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose modification options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The company followed the G-BA's specification of the ACT for both research questions. For research question 1, it did not make a selection; for research question 2, it selected ustekinumab as ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

If necessary for better readability, the present benefit assessment uses the following terms for the patient populations of the research questions presented in Table 4:

- Research question 1: patients who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

- Research question 2: patients who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy

In the following Chapter I 3, research question 2 of the present benefit assessment is addressed first, as the company submitted data for the assessment of the added benefit of risankizumab only for this research question. Research question 1 is then addressed in Chapter I 4.

I 3 Research question 2: patients who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risankizumab (status: 5 October 2022)
- bibliographical literature search on risankizumab (last search on 5 October 2022)
- search in trial registries/trial results databases for studies on risankizumab (last search on 5 October 2022)
- search on the G-BA website for risankizumab (last search on 7 October 2022)

To check the completeness of the study pool:

- search in trial registries for studies on risankizumab (last search on 5 January 2023); for search strategies, see Appendix I A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
M20-259 (SEQUENCE[c])	No	Yes	No	Yes [3]	Yes [4,5]	No

a. Study for which the company was sponsor.
b. References of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

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

The SEQUENCE study is used for the benefit assessment. The study pool concurs with that of the company. The study is described in the following section.

I 3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SEQUENCE	RCT, open-label, parallel	Adult patients with active moderate to severe Crohn's disease[b, c] who have had an inadequate response or were intolerant to TNF-alpha antagonists[d]	Risankizumab (N = 265) ustekinumab (N = 262) Relevant subpopulation thereof[e]: risankizumab (n = 128) ustekinumab (n = 137)	Screening: 35 days Treatment: ▪ 48 weeks or until the occurrence of unacceptable toxicity or discontinuation of therapy as decided by the investigator or the patient[f] Follow-up: 140 days	307 study centres[g] in Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Netherlands, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Spain, Switzerland, Turkey, Ukraine, United Kingdom, United States 9/2020–ongoing Data cut-off: 13 July 2022[h]	Primary: ▪ clinical remission (CDAI < 150) at week 24 ▪ endoscopic remission at week 48[i] Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Defined using the following criteria: CDAI score 220 to 450 at baseline, endoscopic evidence of mucositis documented by an SES-CD of ≥ 6 for ileocolonic or colonic disease, or ≥ 4 for isolated ileal disease, as well as an average daily stool frequency of ≥ 4, and/or an average daily abdominal pain score of ≥ 2 at baseline.
c. The diagnosis must have been established at least 3 months before baseline by means of a documented biopsy. Ulcerative colitis or indeterminate colitis had to be excluded.
d. No minimum dose or duration of use is required to demonstrate intolerance. Inadequate response to biologics is defined as signs and symptoms of persistent active disease (at the investigator's discretion) despite one or more of the following prior therapies: ≥ 6-week induction regimen of infliximab (≥ 5 mg/kg IV in weeks 0, 2, 6), ≥ 4-week induction regimen of adalimumab (single dose of 160 mg SC in week 0, followed by 80 mg SC in week 2 [or single dose of 80 mg SC in week 0, followed by 40 mg SC in week 2]), ≥ 4-week induction regimen of certolizumab pegol (400 mg SC in weeks 0, 2, 4) or recurrence of symptoms during the scheduled maintenance dose after previous success of one of the aforementioned TNF-alpha antagonists. Patients who discontinued TNF-alpha antagonists for any reason other than inadequate response or intolerance were not eligible for the study.
e. Number of randomized patients meeting the criteria of the prespecified data cut-off (interim lock 1)[h].
f. Patients who have completed 48 weeks of treatment with risankizumab can continue treatment with risankizumab for up to 220 weeks in a single-arm extension study. This part of the study is not relevant for the present benefit assessment and is not shown in the following tables.
g. According to Module 4 A; there are discrepancies in the number of countries within Module 4 A and between Module 4 A and the clinical study report.
h. Prespecified data cut-off (interim lock 1) at which approximately 50% of the randomized patients had been treated for at least 24 weeks or had discontinued the study prematurely.
i. The outcome was initially defined as a secondary outcome and was introduced as a primary outcome with protocol version 2 (28 September 2021). The clinical remission at week 48 (CDAI < 150), previously defined as primary outcome, was defined as secondary outcome.

AE: adverse event; CDAI: Crohn's Disease Activity Index; IV: intravenous; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; SC: subcutaneous; SES-CD: Simple Endoscopic Score for Crohn's Disease; TNF: tumour necrosis factor

Table 7: Characteristics of the intervention – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison
SEQUENCE	Risankizumab 600 mg[a] IV at weeks 0, 4 and week 8 Risankizumab 360 mg[a] SC at week 12, then every 8 weeks	Ustekinumab IV weight-dependent once at week 0 ▫ 260 mg (≤ 55 kg) ▫ 390 mg (> 50 kg, ≤ 85 kg) ▫ 520 mg (> 85 kg) Ustekinumab 90 mg SC at week 8, then every 8 weeks
	Required pretreatment ▪ TNF-alpha antagonists (infliximab, adalimumab, certolizumab pegol or a biosimilar) ≥ 8 weeks before baseline[b] **Prohibited prior and concomitant treatment** ▪ surgical abdominal resection ≤ 3 months before baseline or more than 3 abdominal resections in total ▪ biological and/or small low molecular treatmentsc ▪ oral corticosteroidsd: ▫ budesonide > 9 mg/day ▫ beclometasone > 5 mg/day ▫ prednisone or prednisone equivalent > 20 mg/day ▪ IV and intramuscular corticosteroids < 14 days before screening ▪ exclusive enteral nutrition or other parenteral nutrition ≤ 35 days before baseline ▪ IV anti-infectives ≤ 35 days before baseline ▪ oral and intramuscular anti-infectives (unrelated to Crohn's disease) ≤ 14 days before baselinee ▪ oral ciclosporin, tacrolimus or mycophenolate mofetil ≤ 35 days before baseline ▪ faecal microbiota transplantation ≤ 35 days before baseline **Permitted concomitant treatment** ▪ oral aminosalicylates and Crohn's disease-related antibiotics, provided constant dosing was achieved ≥ 14 days before baselinef ▪ immunomodulators, provided they were initiated ≥ 42 days before baseline and the dose has been constant for ≥ 35 daysf	

Table 7: Characteristics of the intervention – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison

a. A previous protocol version had specified an induction dosage of 1200 mg IV every 4 weeks and subsequent 1:1 randomization to 2 risankizumab arms with a maintenance dose of 360 mg every 8 weeks or a maintenance dose of 180 mg every 8 weeks. Based on the approval granted during the course of the study, the dosages in protocol version 2 (28 September 2021) were adjusted to the currently approved dosages.
b. An 8-week washout period is not necessary in the case of proven absence of corresponding drug residues.
c. Except TNF-alpha antagonists.
d. When taking an allowed dosage of corticosteroids, this treatment had to be already in place for ≥ 14 days before baseline and stable for ≥ 7 days before baseline. Patients taking allowed dosages of corticosteroids at baseline must continue treatment with corticosteroids at the baseline dosage for 2 weeks and then reduce this dosage in accordance with a specified schedule. Only in the case of moderate to severe treatment-related toxicity may the dosage be reduced already during the first 2 weeks. In exceptional cases, it is also possible to increase the corticosteroids to the baseline level during the treatment phase. If corticosteroids are initiated or their dosage increased above baseline level, the study medication should only be discontinued if, in the opinion of the investigator, continuation of the study treatment would pose a risk to the study participant.
e. Except for tuberculosis prophylaxis.
f. Dose changes, discontinuation or initiation of these drugs is not permitted during the study. Dose reduction is possible only in cases of moderate to severe treatment-related toxicity. Crohn's disease-related antibiotics may only be discontinued from week 12 at the investigator's discretion.

IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor

Study design and patient population

The SEQUENCE study is an ongoing, open-label RCT comparing risankizumab with ustekinumab in adult patients with active moderate to severe Crohn's disease who have had an inadequate response or were intolerant to TNF-alpha antagonists. The diagnosis must have been established at least 3 months before enrolment.

Disease severity and activity was defined using the following criteria at study start: CDAI score 220 to 450 at baseline; endoscopic evidence of mucositis documented by an SES-CD of ≥ 6 for ileocolonic or colonic disease, or ≥ 4 for isolated ileal disease, as well as an average daily stool frequency of ≥ 4, and/or an average daily abdominal pain score of ≥ 2 (on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe) at baseline recorded by patient diary. For the present benefit assessment, the severity definition using the inclusion criteria of the SEQUENCE study is deemed a sufficient approximation of moderate to severe Crohn's disease.

In order to participate in the study, patients had to have demonstrated lack of response or intolerance to TNF-alpha antagonists at least 8 weeks before baseline (see Table 6 for details). Other prior therapies such as integrin inhibitors or interleukin inhibitors were not allowed in the SEQUENCE study. Patients with current diagnosis of ulcerative colitis or indeterminate colitis were excluded from the study. Furthermore, patients were not allowed to have any manifestations (e.g. abdominal abscesses, toxic megacolon) that could have required surgery

during study participation. Patients who had been treated with corticosteroids for at least 14 days before baseline, with a stable dose for at least 7 days, were eligible to participate in the study (see Table 7 for details on dosing and the regimen for reduction of corticosteroids after randomization).

Patients were randomly allocated to the study arms in a 1:1 ratio. Randomization was stratified by number of previous failed TNF-alpha antagonists (≤ 1, > 1) and baseline corticosteroid use (yes, no). A total of 265 patients were randomized to the risankizumab arm and 262 patients to the ustekinumab arm.

From protocol version 2 onwards, treatment with risankizumab was in compliance with the SPC [6]. Protocol version 1 of the SEQUENCE study dated 23 July 2020 had still specified an induction dosage of 1200 mg, which was not in compliance with the SPC. Protocol version 2 dated 28 September 2021 adjusted the dosage to the currently approved dosage based on the approval granted during the course of the study (see below for the consequences for the analysis population presented). Treatment with ustekinumab was not fully in compliance with the SPC, as the maintenance dose was administered to all patients at an 8-week interval (see below for further details and consequences for the certainty of conclusions).

Initiating corticosteroid therapy or increasing the dose beyond the baseline level as concomitant treatment is in principle not allowed during the study, but this does not necessarily have to lead to discontinuation of the study medication. In these cases, the study medication should only be discontinued if, in the opinion of the investigator, continuation would represent a risk for the study participant.

The duration of treatment is 48 weeks or until the occurrence of unacceptable toxicity or discontinuation of therapy following decision by the physician or patient. Subsequently, patients in the risankizumab arm have the option of continuing treatment with risankizumab for up to 220 weeks in a single-arm extension study.

Primary outcomes of the study are clinical remission (CDAI < 150) at week 24 and endoscopic remission at week 48. Furthermore, patient-relevant outcomes on morbidity, health-related quality of life, and side effects are recorded.

Data cut-offs

In Module 4 A, the company presented results for the prespecified data cut-off 1 (interim lock 1) from 13 July 2022. This data cut-off was planned as soon as approximately 50% of the randomized patients had been treated for at least 24 weeks or had discontinued the study prematurely. At the time point of the data cut-off, these were 135 patients in the risankizumab arm and 137 patients in the ustekinumab arm. This data cut-off is used for the benefit assessment. In principle, results at week 24 are considered; however, according to the

information provided by the company in Module 4 A, analyses are available for side effects outcomes (including mortality) that occurred before 22 June 2022, i.e. possibly also beyond week 24.

Analysis population presented by the company

As already described above, the induction dosage of risankizumab was only adjusted to the currently valid approval with protocol version 2 [6]. The company therefore presented analyses for a prespecified subpopulation that only included patients in the intervention arm with risankizumab treatment that was in compliance with the SPC (N = 128 in the risankizumab arm, N = 137 in the ustekinumab arm). A total of 7 patients randomized to the risankizumab arm under protocol version 1 were therefore not considered in the analyses presented by the company. However, the company's approach to only exclude the 7 patients in the intervention arm from the analyses is not appropriate. Although it is comprehensible in principle to exclude from the analysis patients with treatment that is not in compliance with the SPC, in the present case this potentially leads to an imbalance between intervention and comparator arm in relevant baseline characteristics, which were partly used as stratification factors (e.g. treatment with corticosteroids at baseline, see Table 8). Although these were only few patients, this is relevant in the present data situation in addition to other aspects when analysing the efficacy outcomes. The resulting consequences are described in Section I 3.2.1.

Limitations of the SEQUENCE study

The results of the SEQUENCE study are used for the benefit assessment. However, there are limitations. These uncertainties are described below.

Prior TNF-alpha antagonist therapies

According to the data provided by the company, around 75% of patients had received ≤ 1 previous failed therapy with a TNF-alpha antagonist (see Table 8). Based on these data, it remains unclear whether and, if so, how many patients had not received (documented) previous therapy with a TNF-alpha antagonist (corresponding to < 1). These patients would not be covered by the present therapeutic indication. The company presented no additional information regarding this aspect. Due to the clear inclusion criteria regarding necessary prior therapies as well as no recorded protocol violations for this criterion, it is not assumed that this is a relevant proportion of the included patients. The resulting uncertainty is taken into account in the assessment of the certainty of conclusions, however.

Implementation of the appropriate comparator therapy

The SEQUENCE study used ustekinumab as comparator therapy. In the study, treatment with ustekinumab was induced with a weight-dependent intravenous single dose in compliance with the SPC [7]. 8 weeks after the intravenous induction dose, ustekinumab was administered subcutaneously every 8 weeks at a dose of 90 mg. However, the SPC [8] recommends

treatment every 12 weeks after the first subcutaneous administration of 90 mg ustekinumab. Patients who lose response on a treatment every 12 weeks may benefit from increasing the dosage frequency to 8 weeks. Based on the clinical assessment, these patients may then receive the next dose either every 8 weeks or every 12 weeks. In the SEQUENCE study, ustekinumab was therefore not administered fully in compliance with the SPC. It is unclear to what extent this deviation influences the effects of the patient-relevant outcomes observed in the study. This uncertainty is taken into account in the assessment of the certainty of results.

In summary, on the basis of the effects shown in the SEQUENCE study, at most hints, e.g. of an added benefit, can be derived for all outcomes (see Section I 3.2.2).

Characteristics of the study population

Table 8 shows the characteristics of the patients in the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study **Characteristic** **Category**	**Risankizumab** **N[a] = 128**	**Ustekinumab** **N[a] = 137[b]**
M20-259		
Age [years], mean (SD)	40 (14)	39 (15)
Sex [F/M], %	48/52	55/45
Region, n (%)		
North America	21 (16)	24 (18)
South/Central America	5 (4)	8 (6)
Eastern Europe	21 (16)	25 (18)
Western Europe	44 (34)	45 (33)
Asia	20 (16)	26 (19)
Other	17 (13)	9 (7)
Smoking status, n (%)		
Smoker	36 (28)	25 (18)
Ex-smoker	28 (22)	43 (31)
Never smoker	64 (50)	69 (50)
Alcohol consumption, n (%)		
Current	35 (27)	43 (31)
Former	5 (4)	11 (8)
Never	86 (67)	82 (60)
IBDQ, mean (SD)[c]		
IBDQ total score	118.7 (32.4)	114.1 (30.2)
IBDQ bowel symptoms domain	38.0 (8.8)	36.5 (9.4)
IBDQ systemic symptoms domain	16.0 (5.7)	15.2 (5.1)
IBDQ emotional functioning domain	46.0 (15.0)	44.2 (13.5)
IBDQ social functioning domain	18.7 (7.0)	18.2 (6.7)
SF-36, mean (SD)[d]		
SF-36 PCS	39.2 (7.1)	38.4 (6.8)
SF-36 MCS	38.6 (10.5)	35.9 (9.9)
Stool frequency, daily average, mean (SD)	5.8 (2.8)	5.6 (2.6)
Abdominal pain, daily average, mean (SD)	1.9 (0.6)	1.8 (0.6)
CDAI, mean (SD)	311.4 (64.9)	303.2 (57.5)
SES-CD, mean (SD)	13.8 (7.6)	13.6 (7.2)
Localization of Crohn's disease using the SES-CD, n (%)		
Colon	52 (41)	60 (44)
Ileum	20 (16)	24 (18)
Ileocolon	56 (44)	53 (39)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: risankizumab vs. ustekinumab (multipage table)

Study **Characteristic** **Category**	**Risankizumab** **N[a] = 128**	**Ustekinumab** **N[a] = 137[b]**
Extraintestinal manifestation, n (%)		
Yes	61 (48)	58 (42)
No	67 (52)	79 (58)
Duration of Crohn's disease [years], median [Q1; Q3]	7.8 [4.1; 15.2]	7.5 [3.7; 14.6]
Number of previous failed TNF-alpha antagonists, n (%)		
≤ 1	99 (77)	100 (73)
> 1	29 (23)	37 (27)
Treatment with corticosteroids at baseline, n (%)		
Yes	30 (23)	40 (29)
No	98 (77)	97 (71)
Treatment with immunosuppressants at baseline, n (%)		
Yes	19 (15)	25 (18)
No	109 (85)	112 (82)
Treatment discontinuation, n (%)[e, f]	9 (7)	34 (25)
Study discontinuation, n (%)[g, h]	9 (7)	29 (21)

a. Number of randomized patients. Values that are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Including the patients enrolled under protocol version 1.
c. Data related to n = 115 (risankizumab) and n = 129 (ustekinumab).
d. Data related to n = 116 (risankizumab) and n = 126 (ustekinumab).
e. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were lack of efficacy (2% vs. 13%), discontinuation at the patient's request (3% vs. 4%), and AEs (2% vs. 4%).
f. Treatment discontinuation by week 24 in the intervention vs. control arm: 4 (3%) vs. 20 (15%).
g. Common reasons for study discontinuation in the intervention arm vs. control arm were discontinuation at the patient's request (3% vs. 7%).
h. Study discontinuation by week 24 in the intervention vs. control arm: 3 (2%) vs. 12 (9%).

AE: adverse event; CDAI: Crohn's Disease Activity Index; F: female; IBDQ: Inflammatory Bowel Disease Questionnaire; M: male; MCS: Mental Component Summary; n: number of patients in the category; N: number of randomized patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF-36: Short Form 36 Health Survey; TNF: tumour necrosis factor

The patient characteristics are largely comparable between the treatment arms. In both study arms, the patients' average age was about 40 years, and sex distribution was almost balanced, with slightly more women included in the control arm (55%) than in the intervention arm (48%). The average daily stool frequency was close to 6 and the abdominal pain score was about 2. Treatment with corticosteroids at baseline was higher in the control arm (29%) than in the intervention arm (23%), despite stratification for this characteristic. This is most likely

due to the 7 patients who were not included in the analyses due to risankizumab treatment that was not in compliance with the SPC (see also above).

The proportion of patients with treatment or study discontinuation until the present data cut-off was notably higher in the control arm (25% and 21% respectively) than in the intervention arm (7% each). The proportion of patients with treatment or study discontinuation until week 24 (time point of the analysis of the efficacy outcomes) was also notably higher in the control arm (15% and 9% respectively) than in the intervention arm (3% and 2% respectively). The most frequent reasons for treatment discontinuation were lack of efficacy and discontinuation at the patient's request.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT: risankizumab vs. ustekinumab

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

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

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company stated that the SEQUENCE study was conducted worldwide, including German study centres, and that about 78% of the study population were white participants. Due to the structural equality between the study population and the target population in the therapeutic indication, especially with regard to the clinical parameters, the company assumed that the clinical effects observed in the SEQUENCE study also occur in health care under everyday conditions, and that the study results are therefore transferable to the German health care context. The company added that the subgroup analyses conducted did not show any relevant effect modifications for the subgroup of geographical region.

In the SEQUENCE study, ustekinumab was given at a maintenance dose of 90 mg every 8 weeks. According to the SPC, 2 dosing regimens of ustekinumab are available for maintenance treatment. The dosage is either 90 mg every 12 weeks or 90 mg every 8 weeks if there is an inadequate response. The company considered the results of the SEQUENCE study to be transferable to the German health care context, and justified this by stating that the 8-week dosing regimen in maintenance treatment corresponded to the established treatment standard in Germany and that it could also be assumed that the administration of ustekinumab at 8-week intervals did not result in a relevant underestimation or overestimation of the benefit and/or harm of risankizumab.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - clinical remission (PRO-2: stool frequency and abdominal pain)
  - bowel symptoms (IBDQ subscore of bowel symptoms)
  - systemic symptoms (IBDQ subscore of systemic symptoms)
- Health-related quality of life
  - IBDQ total score
  - SF-36
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Outcomes							
	All-cause mortality[a]	Clinical remission (PRO-2: stool frequency + abdominal pain)	Symptoms (IBDQ: bowel symptoms, systemic symptoms)	Health-related quality of life (IBDQ, SF-36)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Specific AEs
SEQUENCE	Yes	No[c]	No[c]	No[c]	Yes	Yes	Yes	No[d]

a. Deaths were surveyed under AEs.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. No suitable data available; see text below for reasons.
d. No specific AEs were identified based on the AEs which occurred in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; IBDQ: Inflammatory Bowel Disease Questionnaire; PRO: patient-reported outcomes; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey

Outcomes on morbidity and health-related quality of life

Outcome of CDAI not suitable for benefit assessment

The outcome of CDAI used by the company for clinical remission is not suitable for the benefit assessment. This is mainly due to the fact that, in addition to patient-relevant parameters (e.g. PRO-2, see below), this outcome also includes parameters that do not directly represent noticeable changes for the patients (e.g. investigations: haematocrit, body weight). In addition, the G-BA pointed out in its consultation of 30 September 2021 [9] that although the CDAI was an established instrument for quantifying the overall activity of Crohn's disease, the content validity had not been investigated for the target population and no validation studies were available for the threshold values of the CDAI. The European Medicines Agency (EMA) also advises against using the CDAI as an outcome in the therapeutic indication of Crohn's disease [10].

PRO-2

The present benefit assessment uses the PRO-2 (consisting of the symptoms of stool frequency and abdominal pain rated on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe in a patient diary), operationalized as average stool frequency ≤ 2.8/day and average abdominal pain ≤ 1/day and either not worse than at baseline, for the outcome of clinical remission at week 24 (mean value formed over 7 days in each case). This operationalization corresponds to a largely symptom-free condition of the patients and is therefore face valid.

The EMA also recommends the PRO-2 as an outcome in the therapeutic indication of Crohn's disease [10].

It should be noted that individual values for the calculation of the daily average mean may be missing for patients for whom data are available at week 24. According to the statistical analysis plan of the SEQUENCE study, any individual days (up to 3 of the 7 days) that were missing for the calculation of the daily average mean were imputed by the mean of the known values. It is unclear for how many patients individual days were imputed. This is another uncertainty in addition to the overall high proportions of missing values described below.

Health-related quality of life (SF-36 and IBDQ total score) and symptoms (IBDQ subscores of bowel symptoms, systemic symptoms)

In addition to the SF-36, the company presented analyses for the IBDQ. The IBDQ comprises a total of 32 questions on aspects of inflammatory bowel disease. The questionnaire comprises 4 domains, with 10 questions on bowel symptoms, 5 questions on systemic symptoms, 12 questions on emotional functioning and 5 questions on social functioning. Each question can be rated on a scale of 1 to 7, with higher scores indicating a better condition [11,12]. The total score (IBDQ total score) ranges from 32 to 224 points. Separate subscores can be calculated for the 4 domains: bowel symptoms 10 to 70 points; social functioning 5 to 35 points; systemic symptoms 5 to 35 points; emotional functioning 12 to 84 points. The IBDQ is a widely used and validated disease-specific instrument in the present therapeutic indication of Crohn's disease [13-15]. The IBDQ total score is assigned to the outcome category of health-related quality of life. For the IBDQ total score and for the subscores, the company submitted responder analyses for the threshold value ≥ 15% of the respective scale range at week 24. As explained in the *General Methods* of the Institute [1,16], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The responder analyses on the IBDQ submitted by the company thus comply with the requirements of the methods paper and are used for the benefit assessment.

For the SEQUENCE study, there are no patient-relevant outcomes beyond the PRO-2 that reflect the disease-specific symptoms of Crohn's disease. In the present data situation, the 2 subscores of bowel symptoms and systemic symptoms of the IBDQ are therefore used to assess symptoms, in addition to the total score of the IBDQ, which reflects health-related quality of life.

Hospitalization

Disease-related hospitalization is not presented, as it is not clear from the company's dossier how the disease-related events were adjudicated. Overall hospitalization is presented as supplementary information in I Appendix C of the full dossier assessment.

Outcomes on morbidity and health-related quality of life – analyses of the company not suitable for benefit assessment

The information provided by the company shows that, for the efficacy outcomes selected for the benefit assessment, values at the analysis date of 24 weeks are missing to a relevant extent (see Table 11). The company therefore presented 2 analyses with different imputation strategies for the missing values. Independently of this, it made additional assumptions or restricted the analysis population. Overall, the analyses presented by the company show only minor differences between the treatment arms with only partially statistically significant effects depending on the selected imputation strategy. The missing values, the imputation strategies chosen for them, and the assumptions and restrictions of the analysis population are thus relevant to the conclusion in the present data situation. Overall, due to these uncertainties, none of the analyses presented is suitable for the benefit assessment. This is justified below.

Proportion of missing values and imputation strategies chosen by the company

As described in Section I 3.1.2, more patients in the comparator arm discontinued treatment or the study prematurely. However, the proportion of missing values for the patient-reported efficacy outcomes (PRO-2, IBDQ, SF-36) in both treatment arms clearly exceeds the proportion that can be explained by study or treatment discontinuation (see Table 11).

Table 11: Overview of imputed values in the NRI and MI analyses of the company in the relevant outcomes of the SEQUENCE study (research question 2: patients who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy)

Study **Outcome**	**Risankizumab** **N[a] = 128**	**Ustekinumab** **N[a] = 137[b]**
SEQUENCE (at week 24)		
Treatment discontinuation, n (%)	4 (3)	20 (15)
Study discontinuation, n (%)	3 (2)	12 (9)
Clinical remission (PRO-2)[c]		
Imputed values, n (%)	27 (21)	37 (27)
Bowel symptoms (IBDQ)[d]		
Imputed values, n (%)	22 (17)	32 (23)
Systemic symptoms (IBDQ)[d]		
Imputed values, n (%)	23 (18)	32 (23)
Health-related quality of life (IBDQ total score)[d]		
Imputed values, n (%)	23 (18)	33 (24)
Health-related quality of life (SF-36)[d]		
SF-36 PCS		
Imputed values, n (%)	24 (19)	30 (22)
SF-36 MCS		
Imputed values, n (%)	24 (19)	30 (22)

a. Number of randomized patients. Values that are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Including the patients enrolled under protocol version 1.
c. Operationalized as stool frequency ≤ 2.8 and abdominal pain ≤ 1 and either not worse than at baseline.
d. Improvement by ≥ 15% of the scale range.

IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; MI: multiple imputation; n: number of patients in the category; N: number of randomized patients; NRI: non-responder imputation; PCS: Physical Component Summary; PRO: patient-reported outcomes; SF-36: Short Form 36 Health Survey

The company addressed the missing values in its analyses with 2 different imputation strategies. In the main analysis of the company, missing values were mainly imputed by non-responder imputation (NRI). In the sensitivity analysis of the company, missing values were imputed by multiple imputation (MI).

In NRI, patients with missing values are rated as non-responders. However, it cannot be assumed for the SEQUENCE study that the main reason for missing values was non-response. It is unclear how many patients actually discontinued the study due to lack of efficacy by week 24 (time point of analysis of efficacy outcomes). However, at 2% in the intervention arm and 9% in the comparator arm, the proportion of patients who discontinued the study by week 24 is notably lower than the proportion of missing values for the relevant efficacy outcomes (see Table 11). According to the data provided by the company, about 3% of patients in the

intervention arm and about 15% in the comparator arm had discontinued treatment by week 24 (1% versus 6% due to lack of efficacy). The treatment discontinuations thus only partially explain the proportion of missing values. This imputation strategy therefore allows no sufficiently reliable interpretation of the effects in the present data situation with only small effects.

In MI, missing values are imputed several times with data generated from a probability distribution based on the observed values. The results from the data sets with fully imputed values are then pooled using appropriate methods. Although this method is to be preferred in the present data situation, there are such far-reaching limitations here due to the assumptions made by the company as well as the restrictions of the analysis population described below that no reliable interpretation of the results is possible either.

Assumptions for patients taking corticosteroids not appropriate, and limitation of analysis population

In the analyses presented by the company (both NRI and MI), patients who initiated corticosteroid treatment during the study or required corticosteroid treatment beyond their individual baseline level were considered non-responders in all efficacy outcomes. This approach is not appropriate. Initiating corticosteroid therapy or increasing the dose of corticosteroids can be part of the treatment strategy in the present therapeutic indication, and also do not necessarily lead to discontinuation of the study medication in the SEQUENCE study (see also Section I 3.1.2). According to the information provided by the company in Module 4 A, no patients in the intervention arm and 9 patients in the control arm were rated as non-responders due to the use of corticosteroids. However, for 6 of these 9 patients in the comparator arm, complete observations at week 24 are available at least for the CDAI (which includes the PRO-2), according to the clinical study report. Accordingly, these 6 patients should also be included in the analysis with their observed values, provided that they continued to be treated with ustekinumab under corticosteroid therapy. The 3 patients without values at week 24 should be imputed analogously to the respective imputation strategy.

In addition, the 7 patients in the intervention arm who were included under protocol version 1 and thus received a dosage of risankizumab that was not in compliance with the SPC were not taken into account in the analyses of the company (see also Section I 3.1.2). The approach of the company to exclude only the patients in the intervention arm potentially leads to a structural inequality in relevant baseline characteristics (see also Table 8). It is unclear to what extent this influences the results of the efficacy outcomes. Checking this requires analyses that also exclude patients of the comparator arm who were included under protocol version 1.

Overall, the 2 aspects described only affect few patients, but in the present data situation with only small effects, they can have a relevant influence on the observed effects.

Sensitivity analyses conducted by the Institute

In addition to the analyses presented by the company, the Institute conducted sensitivity analyses on the basis of the data presented. However, in addition to the aspects described above, the sensitivity analyses conducted by the Institute have the limitation that no adjustment can be made for the stratification factors (corticosteroid use at baseline and number of previous TNF-alpha antagonist therapies). Due to the only small effects with borderline statistically significant results, the lack of adjustment has a partially relevant influence on the observed effects. Thus, the calculations conducted by the Institute are also not suitable for the benefit assessment.

Conclusion on the outcomes of morbidity and health-related quality of life

The overall picture shows that neither the analyses presented by the company nor the analyses calculated by the Institute are suitable for the benefit assessment. Thus, there are no suitable data for the relevant efficacy outcomes of the categories of morbidity and health-related quality of life. A conclusive assessment of the treatment effects therefore requires further analyses (including subgroup analyses) of the company:

- Patients who initiated corticosteroid therapy or used corticosteroids above their baseline level after the start of the study must be included in the analyses with their observed values, regardless of the chosen imputation strategy, if they still received treatment with ustekinumab. If no values are available for these patients, these values must be imputed in accordance with the imputation strategy used (NRI or MI).
- Further analyses on all efficacy outcomes must exclude the patients enrolled in the comparator arm under protocol version 1, analogously to those in the intervention arm, to achieve better comparability between the treatment arms.

Outcome category of side effects

AEs were recorded in the study from the time point of study drug administration up to 140 days after the last dose of study drug. All AEs that occurred up to data cut-off 1 (interim lock 1) were included in the analyses of the company.

The company presented analyses of AEs, SAEs and severe AEs, each with and without disease-related events. The analyses without disease-related events did not consider the Preferred Terms (PTs) of fistulae, abscesses, stenoses/obstructions, anal fissures, Crohn's disease and intestinal perforations as disease-related events. On the one hand, this selection does not appear to be complete and, on the other, it remains unclear what rationale the company used when selecting the PTs. The analyses without disease-related events are therefore not used for the benefit assessment. In the present data situation, however, the overall rates including the disease-related events can be used. On the one hand, this is due to the fact that, on the basis of the AEs at System Organ Class (SOC) and PT level, it can be ruled out with sufficient

certainty that a higher number of disease-related events in the comparator arm masks possible disadvantages of the intervention with risankizumab (see I Appendix B of the full dossier assessment).

Since the results for all outcomes in the side effects category show no significant effects in favour or to the disadvantage of risankizumab and the respective confidence intervals clearly cover the zero effect, it is not assumed – in contrast to the efficacy outcomes – that the potential structural inequality described above (patients enrolled under protocol version 1) would have a relevant influence on the results. This aspect therefore remains without consequence for the outcomes of the side effects category.

No other specific AEs relevant to the benefit assessment were identified.

I 3.2.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT: risankizumab vs. ustekinumab

Study		Outcomes							
	Study level	All-cause mortality[a]	Clinical remission (PRO-2)	Symptoms (IBDQ: bowel symptoms, systemic symptoms)	Health-related quality of life (IBDQ, SF-36)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Specific AEs
SEQUENCE	L	L	–[c]	–[c]	–[c]	H[d]	H[d]	H[e]	–

a. Deaths were surveyed under AEs.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. No suitable data available; see Section I 3.2.1 for the reasoning.
d. Large difference in the proportion of patients who discontinued the study (7% vs. 21%) for whom it is unclear whether they are included in the analysis.
e. Lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; IBDQ: Inflammatory Bowel Disease Questionnaire; PRO: patient-reported outcomes; RCT: randomized controlled trial; SAE: serious adverse event; SF-36: Short Form (36) Health Survey

The risk of bias is rated as high for the results of all outcomes except the outcome of all-cause mortality. For the SAEs and severe AEs, it is not clear from the data provided by the company

how many of the patients who discontinued the study per treatment arm were actually followed up after study discontinuation and were therefore included in the analyses. As the proportion of patients who discontinued the study differs between the treatment arms (7% versus 21%), the uncertainty described above is taken into account in the risk of bias. The results for SAEs and severe AEs thus have a high risk of bias. The outcome of discontinuation due to AEs also has a high risk of bias. This is due to lack of blinding in subjective recording of outcomes.

Summary assessment of the certainty of conclusions

The overall certainty of conclusions of the SEQUENCE study is limited due to the uncertainties described in Section I 3.1.2 regarding the number of patients who may not be comprised by the present therapeutic indication, and to the fact that the administration of ustekinumab in the control arm was not fully in compliance with the SPC. Irrespective of the low outcome-specific risk of bias in some cases, at most hints, e.g. of added benefit, can therefore be derived on the basis of the available information for all outcomes.

I 3.2.3 Results

Table 13 summarizes the results for the comparison of risankizumab with ustekinumab in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on overall hospitalization are presented as supplementary information in I Appendix C of the full dossier assessment. The results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix B of the full dossier assessment.

Table 13: Results (mortality, side effects) – RCT, direct comparison: risankizumab vs. ustekinumab

Study Outcome category Outcome	Risankizumab		Ustekinumab		Risankizumab vs. ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
SEQUENCE (13 July 2022 data cut-off)					
Mortality (until 22 June 2022)					
All-cause mortality[a]	128	0 (0)		0 (0)	NC
Morbidity (week 24)					
Clinical remission (PRO-2: stool frequency + abdominal pain)	No suitable data available[b]				
Symptoms (IBDQ: bowel symptoms, systemic symptoms)	No suitable data available[b]				
Health-related quality of life (week 24)					
IBDQ	No suitable data available[b]				
SF-36	No suitable data available[b]				
Side effects[c] (until 22 June 2022)					
AEs (supplementary information)	128	97 (75.8)	137	95 (69.3)	–
SAEs	128	10 (7.8)	137	17 (12.4)	0.63 [0.30; 1.32]; 0.222[e]
Severe AEs[d]	128	17 (13.3)	137	20 (14.6)	0.91 [0.50; 1.66]; 0.757[e]
Discontinuation due to AEs	128	2 (1.6)	137	6 (4.4)	0.36 [0.07; 1.74]; 0.202[e]

a. Deaths were surveyed under AEs.
b. See Section I 3.2.1 for the reasoning.
c. Including disease-related events (see Section I 3.2.1).
d. Operationalized as CTCAE grade ≥ 3.
e. Generalized linear model with log link.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; IBDQ: Inflammatory Bowel Disease Questionnaire; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PRO: patient-reported outcomes; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Sections I 3.1.2 and I 3.2.2).

Mortality

All-cause mortality

In the SEQUENCE study, deaths were recorded under AEs. No deaths occurred in either treatment arm. There is no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Clinical remission (PRO-2), symptoms (IBDQ: bowel symptoms, systemic symptoms)

No suitable data are available for the outcome of clinical remission, recorded with the PRO-2, and the outcome of symptoms, recorded with the IBDQ subscores of bowel symptoms and systemic symptoms (see Section I 3.1.1 for the reasoning). In each case, there is no hint of an added benefit of risankizumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score and SF-36

There are no suitable data for the outcome of health-related quality of life, recorded with the IBDQ total score and the SF-36 (see Section I 3.1.1 for the reasoning). In each case, there is no hint of an added benefit of risankizumab in comparison with ustekinumab; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment arms for either of the outcomes of SAEs, severe AEs or discontinuation due to AEs. There is no hint of greater or lesser harm from risankizumab in comparison with ustekinumab for any of them; greater or lesser harm is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present benefit assessment:

- age (≥ 18 to < 40 versus ≥ 40 to < 65 versus ≥ 65 years)
- sex (female versus male)
- disease severity (CDAI ≤ 300 versus > 300)

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 one 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 presented only if there is a statistically significant and relevant effect in at least one subgroup.

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

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

I 3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 14).

Table 14: Extent of added benefit at outcome level: risankizumab vs. ustekinumab

Outcome category **Outcome**	**Risankizumab vs. ustekinumab** **Proportion of events** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: NC p = NC	Lesser/added benefit not proven
Morbidity		
Clinical remission (PRO-2: stool frequency + abdominal pain)	No suitable data available[c]	Lesser/added benefit not proven
Symptoms (IBDQ: bowel symptoms, systemic symptoms)	No suitable data available[c]	Lesser/added benefit not proven
Health-related quality of life		
IBDQ	No suitable data available[c]	Lesser/added benefit not proven
SF-36	No suitable data available[c]	Lesser/added benefit not proven
Side effects		
SAEs	7.8% vs. 12.4% RR: 0.63 [0.30; 1.32] p = 0.222	Greater/lesser harm not proven
Severe AEs	13.3% vs. 14.6% RR: 0.91 [0.50; 1.66] p = 0.757	Greater/lesser harm not proven
Discontinuation due to AEs	1.6% vs. 4.4% RR: 0.36 [0.07; 1.74] p = 0.202	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).
c. See Section I 3.2.1 for the reasoning.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; NC: not calculable; PRO: patient-reported outcomes; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey

I 3.3.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of risankizumab in comparison with ustekinumab

Positive effects	**Negative effects**
–	–
There are no suitable data for the outcomes of morbidity and health-related quality of life.	

Overall, neither positive nor negative effects were shown for the outcome categories of mortality and side effects. There are no suitable data for the outcome categories of morbidity and health-related quality of life.

In summary, the added benefit of risankizumab in comparison with the ACT is not proven for adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy.

The assessment described above deviates from that of the company, which derived a hint of major added benefit.

I 4 Research question 1: patients who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on risankizumab (status: 5 October 2022)
- bibliographical literature search on risankizumab (last search on 5 October 2022)
- search in trial registries/trial results databases for studies on risankizumab (last search on 5 October 2022)
- search on the G-BA website for risankizumab (last search on 7 October 2022)

To check the completeness of the study pool:

- search in trial registries for studies on risankizumab (last search on 5 January 2023); for search strategies, see Appendix I A of the full dossier assessment

In agreement with the company's findings, the check of completeness of the study pool did not identify any studies suitable for a direct comparison of risankizumab versus the ACT for research question 1.

I 4.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of risankizumab in comparison with the ACT in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy. There is no hint of an added benefit of risankizumab in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of risankizumab in comparison with the ACT for adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy, an added benefit of risankizumab is not proven for research question 1.

The assessment concurs with that of the company.

I 5 Probability and extent of added benefit – summary

Table 16 summarizes the result of the assessment of the added benefit of risankizumab in comparison with the ACT.

Table 16: Risankizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to conventional therapy	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]	Added benefit not proven
2	Adults with moderately to severely active Crohn's disease[b] who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-alpha antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-alpha antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or **interleukin inhibitor (ustekinumab)**[c, d]	Added benefit not proven[e]

a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Patients with moderate to severe Crohn's disease who are still eligible for drug therapy (such as biologics) are assumed not to be candidates for surgical resection of affected bowel segments.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose modification options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.
e. The SEQUENCE study only included patients who had an inadequate response to TNF-alpha antagonists. It remains unclear whether the observed effects can be transferred to patients with previous integrin inhibitor or interleukin inhibitor therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-133.html.