Risankizumab (Crohn's disease)

Addendum to Project A22-133 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
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)
MCS	Mental Component Summary
MD	mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effects model with repeated measures
NRI	non-responder imputation
PCS	Physical Component Summary
PRO	patient-reported outcome
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
TNF	tumour necrosis factor

1 Background

On 3 May 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A22-133 (Risankizumab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the check and assessment of the data from a new data cut-off of the SEQUENCE study subsequently submitted by the pharmaceutical company (hereinafter referred to as the “company”) in the commenting procedure, the presentation and analysis of the outcome of steroid-free remission, and the assessment of the suitability of the outcome of disease-specific hospitalizations for the benefit assessment.

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

2 Assessment

For the benefit assessment of risankizumab, the randomized controlled trial (RCT) SEQUENCE was used for research question 2 of the dossier assessment (patients who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy). This study compared risankizumab with ustekinumab. In its dossier [2], the company presented analyses of the study on the first prespecified data cut-off from 13 July 2022. In these analyses, the results for the outcomes on morbidity and health-related quality of life had such far-reaching limitations due to missing values, assumptions made by the company and restrictions of the analysis population that it was not possible to interpret the results with sufficient certainty.

In the context of the commenting procedure, the company now submitted analyses of the SEQUENCE study for the second prespecified data cut-off (HTA interim lock) of 12 January 2023 for research question 2 [3,4]. In accordance with the commission, this data cut-off, the results of the outcome of steroid-free remission as well as the suitability of the outcome of disease-specific hospitalizations are assessed below.

The company still did not provide any data for research question 1 of the dossier assessment (patients who have had an inadequate response to, lost response to, or were intolerant to conventional therapy), so that there are no new aspects compared with the dossier assessment.

2.1 Study characteristics

Detailed characteristics of the SEQUENCE study and of the study population can be found in dossier assessment A22-133 [1]. The following text describes only deviations regarding data cut-off and analysis population that have resulted from the commenting procedure.

Data cut-off and analysis population

In the comments, the company submitted results of the SEQUENCE study for the second prespecified data cut-off (HTA interim lock) of 12 January 2023. This data cut-off was planned 2 months after the approval by the European Commission. At the time of the data cut-off, 88% of the randomized patients (232 patients in the risankizumab arm and 234 patients in the ustekinumab arm) had been on treatment for at least 24 weeks or had discontinued the study prematurely.

The company subsequently submitted analyses on 2 different populations of the SEQUENCE study for this data cut-off, which it referred to as ITT1H-88% population and IQWiG population. As with the analysis population already defined in the dossier, the ITT1H-88% population considers patients who had been on treatment for at least 24 weeks at the time of the data cut-off or who had discontinued the study prematurely, excluding patients in the intervention arm treated with risankizumab according to protocol version 1, which was not in

compliance with the Summary of Product Characteristics (SPC). At the second data cut-off, this population comprised 225 patients in the intervention arm and 234 patients in the comparator arm. In the IQWiG population, on the other hand, only patients who were included in the study from protocol version 2 onwards were considered in both treatment arms (exclusion of 10 patients per treatment arm). In addition, as required in the dossier assessment, the patients were included in the analyses of the efficacy outcomes with their observed values in each case, regardless of whether treatment with corticosteroids was above baseline level (2 patients in the intervention arm and 16 patients in the comparator arm). However, it is unclear whether these patients were still receiving treatment with the study medication at the date of analysis. In accordance with protocol version 2.0, in principle, data were also recorded for the efficacy outcomes after treatment discontinuation (participation in regular visits until the end of the study for all patients who discontinued treatment and did not withdraw consent) and were to be included in the analyses. However, this procedure was adapted in protocol version 3.0 submitted with the comments of the company. This protocol version describes that no data were to be recorded for the efficacy outcomes (in contrast to the data on side effects) after the start of subsequent therapy with biologics or low molecular drugs.

The IQWiG subpopulation comprises 222 patients in the intervention arm and 224 patients in the comparator arm. Overall, it can be established that there is no important difference between the results of the 2 populations. However, the analyses of the IQWiG population address relevant points of criticism from dossier assessment A22-133 and are therefore used for the benefit assessment. The ITT1H-88% population is not considered further.

As in dossier assessment A22-133, results at week 24 are generally used. For the results on the side effects outcomes (including mortality), however, events beyond week 24 are also included in the analyses submitted by the company, provided they had occurred by 9 December 2022 (median observation period in the intervention arm: 49.4 months, in the comparator arm: 44.4 months; for uncertainties in the calculation of the observation period, see Section 2.2.2).

Characteristics of the relevant subpopulation

Table 1 shows the characteristics of the patients in the relevant subpopulation at the second data cut-off.

Table 1: 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] = 222**	**Ustekinumab** **N[a] = 224**
SEQUENCE (12 January 2023 data cut-off)		
Age [years], mean (SD)	38 (13)	38 (14)
Sex [F/M], %	45/55	50/50
Region, n (%)		
North America	29 (13)	29 (13)
South/Central America	15 (7)	17 (8)
Eastern Europe	32 (14)	31 (14)
Western Europe	86 (39)	80 (36)
Asia	41 (18)	49 (22)
Other	19 (9)	18 (8)
Smoking status, n (%)		
Smoker	55 (25)	49 (22)
Ex-smoker	47 (21)	58 (26)
Never smoker	120 (54)	117 (52)
Alcohol consumption, n (%)		
Current	62 (28)	68 (30)
Former	11 (5)	21 (9)
Never	145 (65)	133 (59)
IBDQ, mean (SD)[b]		
IBDQ total score	115.8 (34.1)	116.7 (30.7)
IBDQ subscores		
IBDQ bowel symptoms domain	37.0 (9.8)	37.2 (9.4)
IBDQ systemic symptoms domain	15.7 (5.7)	15.6 (5.1)
IBDQ emotional functioning domain	45.0 (14.9)	45.5 (13.8)
IBDQ social functioning domain	18.2 (7.2)	18.4 (6.6)
SF-36, mean (SD)[c]		
SF-36 Physical Component Summary (PCS)	38.8 (7.0)	38.4 (6.7)
SF-36 Mental Component Summary (MCS)	37.2 (10.8)	36.6 (10.3)
Stool frequency [daily average], mean (SD)[d]	5.5 (2.7)	5.6 (2.6)
Abdominal pain [daily average], mean (SD)[d]	2.0 (0.5)	1.9 (0.6)
CDAI, mean (SD)[d]	312.5 (62.5)	309.3 (62.1)
SES-CD, mean (SD)	13.7 (7.3)	14.1 (7.6)

Table 1: 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] = 222**	**Ustekinumab** **N[a] = 224**
Localization of Crohn's disease using the SES-CD, n (%)		
Colon	87 (39)	91 (41)
Ileum	36 (16)	35 (16)
Ileocolon	99 (45)	98 (44)
Extraintestinal manifestation, n (%)		
Yes	104 (47)	97 (43)
No	118 (53)	127 (57)
Duration of Crohn's disease [years], median [Q1; Q3]	7.3 [3.5; 13.3]	7.4 [2.9; 13.2]
Number of previous failed treatments with TNF inhibitors, n (%)		
0	1 (< 1)	1 (< 1)
1	167 (75)	171 (76)
> 1	54 (24)	52 (23)
Treatment with corticosteroids, n (%)		
Yes	52 (23)	59 (26)
Thereof topical	ND	
No	170 (77)	165 (74)
Treatment with immunosuppressants, n (%)		
Yes	29 (13)	43 (19)
No	193 (87)	181 (81)
Treatment discontinuation, n (%)[e, f]	20 (9)	52 (23)
Study discontinuation, n (%)[g, h]	21 (10)	40 (18)

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. Data related to N = 206 (risankizumab) and N = 216 (ustekinumab).
c. Data related to N = 207 (risankizumab) and N = 211 (ustekinumab).
d. Data related to N = 218 (risankizumab) and N = 222 (ustekinumab).
e. Common reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages relate to the randomized patients) were lack of efficacy (2% vs. 12%), discontinuation at the patient's request (2% vs. 5%), and AEs (3% vs. 4%).
f. Treatment discontinuation by week 24 in the intervention arm vs. control arm: 7 (3%) vs. 34 (15%).
g. The most common reason for study discontinuation in the intervention arm vs. the control arm (percentages relate to the randomized patients) was discontinuation at the patient's request (3% vs. 7%).
h. Study discontinuation by week 24 in the intervention arm vs. control arm: 2 (1%) vs. 17 (8%).

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; Q1: first quartile; Q3: third quartile; 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 still largely comparable between the treatment arms at the second data cut-off. The difference in the proportion of patients receiving treatment with corticosteroids at baseline is less pronounced in the IQWiG population (23% vs. 26%) than in the ITT1H-50% population (23% vs. 29%).

In its subsequent submission, the company provided information on the exact number of previous failed treatments with a tumour necrosis factor (TNF)-alpha antagonist. Only one patient per study arm (< 1%) had not received previous failed treatment with a TNF-alpha antagonist.

The proportion of patients with treatment or study discontinuation until the present data cut-off is still notably higher in the control arm (23% and 18%) than in the intervention arm (9% and 10%). The proportion of patients with treatment or study discontinuation until week 24 (time point of the analysis of the outcomes on the benefit side) is also still notably higher in the control arm (15% and 8%) than in the intervention arm (3% and 1%). The most frequent reasons for treatment discontinuation were lack of efficacy and discontinuation at the patient's request.

2.2 Results on added benefit

2.2.1 Outcomes included

The choice of patient-relevant outcomes included in the assessment in the present addendum corresponds to the choice made in dossier assessment A22-133.

Outcomes on morbidity and health-related quality of life

Proportion of missing values and imputation strategies chosen by the company

As described in the dossier assessment, more patients in the comparator arm had discontinued treatment or the study prematurely at the first data cut-off on 13 July 2022. The proportion of missing values for the patient-reported efficacy outcomes (PRO-2, Inflammatory Bowel Disease Questionnaire [IBDQ], Short Form 36 Health Survey [SF-36]) was notably higher in both treatment arms than the proportion that could be explained by study or treatment discontinuation, despite the fact that further regular observation had been planned initially for patients who discontinued treatment (also under subsequent therapy) (see protocol amendment version 3.0 above). The high proportion of missing values can still be seen at the second data cut-off of 12 January 2023 assessed here (see Table 2).

Table 2: Overview of imputed values in the NRI and MI analyses of the company for individual outcomes of the SEQUENCE study

Study **Outcome**	**Risankizumab** **N = 222**	**Ustekinumab** **N = 224**
SEQUENCE (at week 24; 12 January 2023 data cut-off)		
Treatment discontinuation, n (%)	7 (3.2)	34 (15.2)
Study discontinuation, n (%)	2 (0.9)	17 (7.6)
Clinical remission (PRO-2)[a]		
Imputed values, n (%)	42 (18.9)	50 (22.3)
Bowel symptoms (IBDQ)[b]		
Imputed values, n (%)	31 (14.0)	41 (18.3)
Systemic symptoms (IBDQ)[b]		
Imputed values, n (%)	32 (14.4)	42 (18.8)
Health-related quality of life (IBDQ total score)[b]		
Imputed values, n (%)	32 (14.4)	43 (19.2)
Health-related quality of life (SF-36)	Responder analyses unsuitable[c]	

a. Operationalized as average daily stool frequency ≤ 2.8 and average daily abdominal pain ≤ 1 (on a 0–3 scale where 0 = no pain, 1 = mild, 2 = moderate, 3 = severe) and either not worse than at baseline.
b. Operationalized as an improvement by ≥ 15% of the scale range.
c. Responder analyses are unsuitable, so no imputed values are provided; see following text section for the rationale.

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

As described in dossier assessment A22-133, it cannot be necessarily assumed for the SEQUENCE study that the main reason for missing values was non-response [1]. In the present data situation, the imputation of missing values by means of multiple imputation (MI) is therefore preferable to non-responder imputation (NRI). The present addendum therefore uses the analyses with imputation of the missing values by MI for the outcomes of morbidity and health-related quality of life.

The limitations described in the dossier assessment with regard to the assumptions made by the company and the restrictions of the analysis population were addressed in the analyses of the relevant subpopulation, which the company submitted with its comments (see also Section 2.1). This approach, as well as the new data cut-off with notably more patients, has resulted in more robust and therefore interpretable results for the outcomes on morbidity and health-related quality of life. Based on the information in the dossier and in the comments, it is unclear which response criterion the company used for the responder analyses for the SF-36, however. Although the company described that it had used a response criterion

corresponding to 15% of the scale range ("IQWiG criterion"), it did not specify which scale range it had used as a basis and which score resulted from this as the 15% response criterion. The responder analyses for the SF-36 are therefore not used for the benefit assessment. For the responder analyses of the IBDQ, the company also did not specify the exact score of the response criteria, but it provided a comprehensible description of the scale ranges it had used as a basis for calculating the 15% response criterion. It is therefore assumed that the response criteria used correspond to the specifications of the *General Methods* of the Institute [5]; and the responder analyses of the IBDQ are used for the benefit assessment. For the SF-36, the analyses based on a mixed-effects model with repeated measures (MMRM) are used instead. The estimated effect represents the difference in changes between treatment groups at week 24. To assess clinical relevance, a standardized mean difference (SMD) analogous to Hedges' g is determined using the mean difference (MD) estimated from the MMRM analysis and the associated confidence interval (CI). Since the company did not calculate the SMD on the basis of the estimated MD, the Institute conducted its own calculations.

It should be noted that no analyses with MI are available for the components of the PRO-2 (stool frequency and abdominal pain). Subgroup analyses on outcomes of morbidity and health-related quality of life with MI are also not available (see also Section 2.2.4).

Steroid-free remission

The outcome of steroid-free remission, operationalized as average daily stool frequency ≤ 2.8 and average daily abdominal pain ≤ 1 and either not worse than at baseline, with concomitant steroid freedom at week 24, is not suitable for the benefit assessment. This is due to the fact that it remains unclear how many patients in the SEQUENCE study were treated exclusively with topical corticosteroids (with possible local side effects versus possible systemic side effects under oral administration). The patient relevance of the operationalization for steroid freedom presented here thus remains unclear. The results are presented as supplementary information in Appendix B. When interpreting the results, it should also be noted that only 25% of patients were treated with corticosteroids at baseline.

Hospitalization

Disease-specific hospitalization and overall hospitalization

For the outcome of disease-specific hospitalization, it was not clear from the company's dossier how the disease-specific events were adjudicated. In its comments, the company clarified that this was done exclusively by the investigators and also provided a list of the Preferred Terms (PTs) on which the event of disease-specific hospitalization was based. This shows that the underlying PTs are missing for 6 of the 20 events in the comparator arm. It also remains unclear, for example, why the company considered the PT diarrhoea as a disease-specific event in the outcome of disease-specific hospitalization, while this PT was not rated as a disease-specific event in the analyses of AEs. Overall, it is not sufficiently ensured that the

outcome of disease-specific hospitalization actually reflects predominantly severe Crohn's disease-related events. The outcome is therefore not used for the benefit assessment. Furthermore, it should be noted that data on hospitalization (in the context of the recording on side effects) were recorded up to 20 weeks after treatment discontinuation (or even up to 20 weeks after study discontinuation if possible) and were to be included in the analyses. It can therefore be assumed that data under subsequent therapy were also included in the analyses, although it remains unclear whether patients may have been hospitalized to initiate subsequent therapies; however, no information is available on the subsequent therapies used after treatment discontinuation. This also applies to the outcome of overall hospitalization, which is also substantially influenced by the potentially disease-specific events. Thus, the results for the outcome of overall hospitalization cannot be meaningfully interpreted and are therefore not presented either.

Outcomes on side effects

Overall rates including disease-related events unsuitable for the benefit assessment

Analogous to its dossier, the company presented analyses of adverse events (AEs), serious AEs (SAEs) and severe AEs, each including and excluding disease-related events, in the context of the comments. The dossier assessment criticized that the selection of events considered by the company to be disease-related does not appear to be complete and that it remains unclear which rationale was used by the company to select the corresponding events. These points of criticism were not addressed in the comments of the company. Therefore, the analyses presented by the company excluding disease-related events are still not suitable for the benefit assessment.

Dossier assessment A22-133 used the overall rates including disease-related events as a makeshift, as it could be ruled out with sufficient certainty on the basis of the AEs at the level of System Organ Class (SOC) and PTs that possible disadvantages of the intervention with risankizumab were masked by a higher number of disease-related events in the comparator arm. In the present data situation, however, it is not possible to use the overall rates including disease-related events. This is due to the fact that the proportion of disease-related events is now high at the second data cut-off (especially SOC gastrointestinal disorders and PT Crohn's disease; see Appendix C). This influences the results in the AE outcomes in favour of risankizumab. The overall rates including disease-related events are therefore not suitable for the benefit assessment in the present situation. To nevertheless enable a balancing of benefit and harm (see Section 2.3.2), an approximation of the overall rates of SAEs and severe AEs excluding disease-related events is considered despite the limitations described above. These analyses do not take into account at least some disease-related events (including PT Crohn's disease), allowing an approximate estimate of the effects in the outcomes on SAEs and severe AEs. In addition, no hints of greater harm from risankizumab result from the results on other specific AEs. For the outcome of discontinuation due to AEs, the company did not provide any

analyses excluding disease-related events; in addition to the limitations described, the analyses on AEs are therefore incomplete. Besides, there are uncertainties as to how many of the patients who discontinued the study per treatment arm were actually followed up after study discontinuation (see Section 2.2.2). The overall rates excluding disease-related events for the outcomes of SAEs and severe AEs are thus subject to very high uncertainty in the overall consideration and are only presented as supplementary information in Appendix A.

2.2.2 Risk of bias

The risk of bias across outcomes for the SEQUENCE study is rated as low (see dossier assessment A22-133).

Table 3 describes the risk of bias for the results of the relevant outcomes.

Table 3: Risk of bias across outcomes and outcome-specific risk of bias – RCT: risankizumab vs. ustekinumab

Study	Study level	Outcomes							
		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	H[c]	H[c]	H[c]	–[d]	–[d]	–[d]	–[e]

a. Deaths were recorded within the framework of AEs.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. High proportion of imputed (cf. Table 2) or missing values as well as lack of blinding in subjective recording of outcomes.
d. No suitable data available; see Section 2.2.1 for the reasoning.
e. No specific AEs identified based on the AEs occurring 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

The risk of bias of the result on the outcome of all-cause mortality is rated as low. The risk of bias of the results for the outcomes of the categories of morbidity and health-related quality of life is rated as high in each case due to the high proportion of imputed or missing values (see Table 2) as well as the lack of blinding in subjective recording of outcomes. As described in Section 2.2.1, the outcomes of SAEs, severe AEs and discontinuation due to AEs are not used to derive an added benefit. The results on the overall rates excluding disease-related

events are only considered as supplementary information. Therefore, the risk of bias is not assessed for the results on these outcomes. It should be noted, however, that for the results on SAEs and severe AEs, it is still not clear from the data subsequently submitted by the company how many of the patients who discontinued the study per treatment arm were actually followed up after discontinuing the study. As the proportion of patients who discontinued the study differs between the treatment arms (10% versus 18%), this may result in a difference in the duration of follow-up observation between the treatment arms. This might not be reflected in the data provided by the company on the duration of follow-up observation, as these were not based on actually observed follow-up observation periods, but were – at least in part – calculated fictitiously by assuming a follow-up observation of 140 days after study discontinuation. This uncertainty described in the dossier assessment thus still exists.

Summary assessment of the certainty of conclusions

As described in Section 2.1, only a non-relevant proportion of the included patients (< 1%) had not received previous failed treatment with a TNF-alpha antagonist and are therefore not included in the present therapeutic indication. The uncertainty described in dossier assessment A22-133, which resulted from the unclear proportion of corresponding patients, therefore no longer applies.

However, there is still the uncertainty described in the dossier assessment regarding the administration of ustekinumab in the control arm, which was not fully in compliance with the SPC. The overall certainty of conclusions of the SEQUENCE study is therefore still limited. Thus, at most hints, e.g. of an added benefit, can be determined for all outcomes on the basis of the available information.

2.2.3 Results

Table 4 and Table 5 summarize 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 the overall rates of AEs excluding disease-related events are presented as supplementary information in Appendix A. The results on the outcome of steroid-free remission are presented as supplementary information in Appendix B. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in Appendix C.

Table 4: Results (mortality, morbidity, and health-related quality of life, dichotomous) – 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[a]
SEQUENCE (12 January 2023 data cut-off)					
Mortality (until 9 December 2022)					
All-cause mortality[b]	222	0 (0.0)	224	0 (0.0)	–
Morbidity (at week 24)[c]					
Clinical remission (PRO-2)[d]	222	138 (62.3)	224	107 (47.7)	1.30 [1.09; 1.55]; 0.004
Stool frequency				ND[e]	
Abdominal pain				ND[e]	
Bowel symptoms (IBDQ)[f]	222	180 (80.9)	224	142 (63.5)	1.27 [1.13; 1.44]; < 0.001
Systemic symptoms (IBDQ)[f]	222	155 (70.0)	224	142 (63.4)	1.11 [0.97; 1.28]; 0.126
Health-related quality of life (at week 24)[c]					
IBDQ total score[f]	222	167 (75.0)	224	134 (59.7)	1.25 [1.09; 1.44]; 0.002
Bowel symptoms (IBDQ)[f]	222	180 (80.9)	224	142 (63.5)	1.27 [1.13; 1.44]; –
Emotional functioning (IBDQ)[f]	222	137 (61.8)	224	112 (50.0)	1.24 [1.04; 1.47]; –
Social functioning (IBDQ)[f]	222	161 (72.5)	224	136 (60.5)	1.19 [1.04; 1.37]; –
Systemic symptoms (IBDQ)[f]	222	155 (70.0)	224	142 (63.4)	1.11 [0.97; 1.28]; –

a. RR, CI and p-value: generalized linear model with log link; adjusted for number of previous failed treatments with TNF-alpha antagonists (≤ 1, > 1) and corticosteroid use at baseline (yes, no).
b. Deaths were recorded within the framework of AEs.
c. Missing values were imputed by MI; cf. Table 2.
d. Operationalized as average daily stool frequency ≤ 2.8 and average daily abdominal pain ≤ 1 (on a 0–3 scale where 0 = no pain, 1 = mild, 2 = moderate, 3 = severe) and either not worse than at baseline.
e. See Section 2.2.1 for the rationale; results of the NRI analysis (RR [95% CI]; p-value): clinical remission (PRO-2): 1.28 [1.05; 1.55]; 0.013; stool frequency: 1.27 [1.07; 1.50]; 0.007; abdominal pain: 1.19 [1.02; 1.37]; 0.023.
f. Operationalized as an improvement by ≥ 15% of the scale range (IBDQ total score: 32 to 224 points; bowel symptoms: 10 to 70 points; systemic symptoms: 5 to 35 points; social functioning: 5 to 35 points; emotional functioning: 12 to 84 points).

CI: confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; MI: multiple imputation; n: number of patients with (at least one) event; N: number of analysed patients; PCS: Physical Component Summary; PRO: patient-reported outcome; RR: relative risk; SF-36: Short Form 36 Health Survey; TNF: tumour necrosis factor

Table 5: Results (morbidity, continuous) – RCT, direct comparison: risankizumab vs. ustekinumab

Study Outcome category Outcome	Risankizumab			Ustekinumab			Risankizumab vs. ustekinumab
	N[a]	Values at baseline mean (SD)	Change at week 24 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at week 24 mean[b] (SE)	MD [95% CI]; p-value[b]
SEQUENCE (12 January 2023 data cut-off)							
Health-related quality of life							
SF-36 PCS	187	38.8 (7.0)	10.1 (0.6)	183	38.4 (6.7)	6.8 (0.6)	3.35 [1.97; 4.73]; < 0.001 SMD [95% CI][c]: 0.49 [0.29; 0.70]
SF-36 MCS[d]	187	37.2 (10.8)	8.1 (0.7)	183	36.6 (10.3)	6.1 (0.7)	1.91 [0.12; 3.69]; 0.036 SMD [95% CI][c]: 0.22 [0.01; 0.42]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Mean and SE (change at week 24 per treatment group) as well as MD, CI and p-value (group comparison): MMRM, adjusted for baseline value and number of previous failed treatments with TNF-alpha inhibitors (≤ 1, > 1), and corticosteroid use at baseline (yes, no). Effect represents the difference between treatment groups in changes from baseline to week 24.
c. Institute's calculation based on MD and CI of the MMRM.
d. No data are available on the SF-36 subscales.

CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form 36 Health Survey; SMD: standardized mean difference

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.2.2).

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)

For the outcome of clinical remission, recorded with the PRO-2, a statistically significant difference between treatment groups was found in favour of risankizumab in comparison with ustekinumab. This difference was no more than marginal, however (see Section 2.3.1). There

is no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome of clinical remission; an added benefit is therefore not proven.

Bowel symptoms (IBDQ)

For the outcome of bowel symptoms, recorded with the corresponding IBDQ subscore, there was a statistically significant difference between treatment groups in favour of risankizumab in comparison with ustekinumab. There is a hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome of bowel symptoms.

Systemic symptoms (IBDQ)

For the outcome of systemic symptoms, recorded with the corresponding IBDQ subscore, no statistically significant difference between treatment groups was found. There is no hint of an added benefit of risankizumab in comparison with ustekinumab for the outcome of systemic symptoms; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

For health-related quality of life, recorded with the IBDQ total score, there was a statistically significant difference between treatment groups in favour of risankizumab in comparison with ustekinumab. There is a hint of an added benefit of risankizumab in comparison with ustekinumab for the IBDQ total score.

SF-36 Physical Component Summary (PCS)

For health-related quality of life, recorded with the SF-36 PCS, there was a statistically significant difference between treatment groups in favour of risankizumab in comparison with ustekinumab. The 95% CI for the SMD was fully outside the irrelevance range [−0.2; 0.2]. This is interpreted to be a relevant effect. There is a hint of an added benefit of risankizumab in comparison with ustekinumab for the SF-36 PCS.

SF-36 Mental Component Summary (MCS)

For health-related quality of life, recorded with the SF-36 MCS, there was a statistically significant difference between treatment groups in favour of risankizumab in comparison with ustekinumab. However, the 95% CI of the SMD was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the observed effect was relevant. There is no hint of an added benefit of risankizumab in comparison with ustekinumab for the SF-36 MCS; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs and discontinuation due to AEs

No suitable data are available for side effects outcomes (see Section 2.2.1).

2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present addendum:

- age (≥ 18 to < 40 versus ≥ 40 to < 65 versus ≥ 65 years)
- sex (female versus male)
- disease severity(Crohn's Disease Activity Index ≤ 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.

As described in Section 2.2.1, there are no subgroup analyses with imputation of missing values by MI and thus no suitable subgroup analyses for the outcomes on morbidity and health-related quality of life.

2.3 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 [5].

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.

2.3.1 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 2.2 (see Table 6).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Clinical remission (PRO-2)

The outcome of clinical remission (PRO-2) is composed of the outcomes of stool frequency and abdominal pain. At study start, the average daily stool frequency of 5.5 was below the

increase of ≥ 7 stools from baseline for the definition as a severe AE according to the Common Terminology Criteria for Adverse Events (CTCAE) (see Table 1). The average daily abdominal pain was 2 on the 0 to 3 scale used, corresponding to "moderate" severity. Therefore, the outcome of clinical remission (PRO-2) is assigned to the outcome category of non-serious/non-severe symptoms.

Bowel symptoms (IBDQ) and systemic symptoms (IBDQ)

For the outcomes of bowel symptoms (IBDQ) and systemic symptoms (IBDQ), no sufficient severity data are available which would allow classifying them as serious/severe. Both outcomes are therefore assigned to the outcome category of non-serious/non-severe symptoms.

Table 6: Extent of added benefit at outcome level: risankizumab vs. ustekinumab (multipage table)

Outcome category **Outcome**	**Risankizumab vs. ustekinumab** **Proportion of events (%) or mean** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser/added benefit not proven
Morbidity		
Clinical remission (PRO-2)[c]	62.3% vs. 47.7% RR: 1.30 [1.09; 1.55] RR: 0.77 [0.65; 0.92][d] p = 0.004	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser/added benefit not proven[e]
Bowel symptoms (IBDQ)[f]	80.9% vs. 63.5% RR: 1.27 [1.13; 1.44] RR: 0.79 [0.69; 0.88][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Systemic symptoms (IBDQ)[f]	70.0% vs. 63.4% RR: 1.11 [0.97; 1.28] p = 0.126	Lesser/added benefit not proven

Table 6: Extent of added benefit at outcome level: risankizumab vs. ustekinumab (multipage table)

Outcome category **Outcome**	**Risankizumab vs. ustekinumab** **Proportion of events (%) or mean** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
IBDQ total score[f]	75.0% vs. 59.7% RR: 1.25 [1.09; 1.44] RR: 0.80 [0.69; 0.92][d] p = 0.002 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
SF-36 Physical Component Summary (PCS)	Mean: 10.1 vs. 6.8 MD: 3.35 [1.97; 4.73] p < 0.001 SMD: 0.49 [0.29; 0.70][g] probability: "hint"	Outcome category: health-related quality of life $0.20 < CI_L \leq 0.30$ added benefit, extent: "minor"
SF-36 Mental Component Summary (MCS)	Mean: 8.1 vs. 6.1 MD: 1.91 [0.12; 3.69] p = 0.036 SMD: 0.22 [0.01; 0.42][g]	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data[h]	Greater/lesser harm not proven
Severe AEs	No suitable data[h]	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data[h]	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. Operationalized as average daily stool frequency ≤ 2.8 and average daily abdominal pain ≤ 1 (on a 0–3 scale where 0 = no pain, 1 = mild, 2 = moderate, 3 = severe) and either not worse than at baseline.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Operationalized as an improvement by ≥ 15% of the scale range.
g. If the CI for the SMD is fully outside the irrelevance range [–0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
h. See Section 2.2.1 for the rationale.

AE: adverse event; CI: confidence interval; CI_L: lower limit of the confidence interval; CI_u: upper limit of the confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; PRO: patient-reported outcome; RR: relative risk; SAE: serious adverse event; SF-36: Short Form 36 Health Survey

2.3.2 Overall conclusion on added benefit

Table 7 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 7: Positive and negative effects from the assessment of risankizumab in comparison with ustekinumab

Positive effects	**Negative effects**
Morbidity Non-serious/non-severe symptoms ▪ Bowel symptoms (IBDQ): hint of an added benefit – extent: “minor”	–
Health-related quality of life ▪ IBDQ total score: hint of an added benefit – extent: “minor” ▪ SF-36 Physical Component Summary (PCS): hint of an added benefit – extent: “minor”	–
No suitable data are available for side effects outcomes.	
IBDQ: Inflammatory Bowel Disease Questionnaire; PCS: Physical Component Summary; SF-36: Short Form 36 Health Survey	

Overall, the second data cut-off of the SEQUENCE study showed exclusively positive effects of risankizumab in comparison with ustekinumab. For the outcome of bowel symptoms (IBDQ) in the outcome category of non-serious/non-severe symptoms, there is a hint of minor added benefit. For the IBDQ total score and the SF-36 PCS in the outcome category of health-related quality of life, there is a hint of minor added benefit in each case. No usable data are available for side effects outcomes. From the available analyses, however, relevantly greater harm from risankizumab can be excluded with a high degree of probability, so that the positive effects are not called into question.

In summary, there is a hint of minor added benefit of risankizumab in comparison with the appropriate comparator therapy for adults 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.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on added benefit of risankizumab drawn in dossier assessment A22-133 for research question 2: There is a hint of minor added benefit of risankizumab in comparison with the appropriate comparator therapy for adults 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.

For research question 1, there is no change in comparison with dossier assessment A22-133.

The following Table 8 shows the result of the benefit assessment of risankizumab under consideration of dossier assessment A22-133 and the present addendum.

Table 8: 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]	Hint of minor added benefit[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 G-BA decides on the added benefit.

3 References

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Appendix A Supplementary presentation of results on the overall rates of side effects excluding disease-related events

Table 9: Results (side effects) – RCT, direct comparison: risankizumab vs. ustekinumab

Study Outcome category Outcome	Risankizumab N	Risankizumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Risankizumab vs. ustekinumab RR [95% CI]; p-value[a]
SEQUENCE (12 January 2023 data cut-off)					
Side effects (9 December 2022 data cut-off)[b]					
AEs (supplementary information)	222	174 (78.4)	224	155 (69.2)	–
SAEs	222	14 (6.3)	224	20 (8.9)	0.71 [0.37; 1.36]; 0.300
Severe AEs[c]	222	24 (10.8)	224	26 (11.6)	0.93 [0.55; 1.57]; 0.790
Discontinuation due to AEs				ND[d]	

a. RR, CI and p-value: generalized linear model with log link; unadjusted.
b. Excluding disease-related events; see Section 2.2.1 for the justification of the approach.
c. Operationalized as CTCAE grade ≥ 3.
d. For the outcome of discontinuation due to AEs, the company did not provide any analyses excluding disease-related events.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Appendix B Supplementary presentation of results on morbidity (steroid-free remission)

Table 10: Results (morbidity) – 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[a]
SEQUENCE (12 January 2023 data cut-off)					
Morbidity (week 24)					
Steroid-free remission (PRO-2)[b, c]	222	128 (57.5)	224	93 (41.7)	1.36 [1.11; 1.65]; 0.003

a. RR, CI and p-value: generalized linear model with log link; adjusted for number of previous failed treatments with TNF-alpha antagonists (≤ 1, > 1) and corticosteroid use at baseline (yes, no).
b. Operationalized as average daily stool frequency ≤ 2.8 and average daily abdominal pain ≤ 1 (on a 0–3 scale where 0 = no pain, 1 = mild, 2 = moderate, 3 = severe) and either not worse than at baseline, and concomitant steroid freedom.
c. Missing values were imputed by MI (risankizumab vs. ustekinumab): 42 (18.9%) vs. 52 (23.2%).

CI: confidence interval; MI: multiple imputation; n: number of patients with (at least one) event; N: number of analysed patients; NRI: non-responder imputation; PRO: patient-reported outcome; RCT: randomized controlled trial; RR: relative risk; TNF: tumour necrosis factor

Appendix C 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): events which occurred in at least 10% of patients in one study arm
- overall rates of severe AEs (e.g. 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

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

Table 11: Common AEs[a] – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Patients with event n (%)	
SOC[b] PT[b]	**Risankizumab N = 222**	**Ustekinumab N = 224**
SEQUENCE (12 January 2023 data cut-off)		
Overall rate of AEs[c] (until 9 December 2022)	179 (80.6)	166 (74.1)
Blood and lymphatic system disorders	17 (7.7)	21 (9.4)
Anaemia	8 (3.6)	15 (6.7)
Gastrointestinal disorders	65 (29.3)	77 (34.4)
Crohn's disease	14 (6.3)	30 (13.4)
Diarrhoea	10 (4.5)	4 (1.8)
General disorders and administration site conditions	32 (14.4)	24 (10.7)
Fatigue	10 (4.5)	3 (1.3)
Pyrexia	17 (7.7)	7 (3.1)
Infections and infestations	96 (43.2)	81 (36.2)
COVID-19	41 (18.5)	37 (16.5)
Injury, poisoning and procedural complications	9 (4.1)	11 (4.9)
Investigations	32 (14.4)	31 (13.8)
Metabolism and nutrition disorders	17 (7.7)	18 (8.0)
Musculoskeletal and connective tissue disorders	31 (14.0)	35 (15.6)
Arthralgia	10 (4.5)	17 (7.6)
Nervous system disorders	25 (11.3)	16 (7.1)
Headache	11 (5.0)	9 (4.0)
Respiratory, thoracic and mediastinal disorders	14 (6.3)	12 (5.4)
Skin and subcutaneous tissue disorders	30 (13.5)	28 (12.5)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken without adaptation from the data subsequently submitted by the company.
c. Including disease-related events.

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 12: Common SAEs[a] – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Patients with event n (%)	
SOC[b] PT[b]	**Risankizumab N = 222**	**Ustekinumab N = 224**
SEQUENCE (12 January 2023 data cut-off)		
Overall rate of SAEs[c] (until 9 December 2022)	19 (8.6)	34 (15.2)
Gastrointestinal disorders	8 (3.6)	21 (9.4)
Crohn's disease	3 (1.4)	10 (4.5)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC notation taken without adaptation from the data subsequently submitted by the company.
c. Including disease-related 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; SAE: serious adverse event; SOC: System Organ Class

Table 13: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: risankizumab vs. ustekinumab

Study	Patients with event n (%)	
SOC[b] PT[b]	**Risankizumab N = 222**	**Ustekinumab N = 224**
SEQUENCE (12 January 2023 data cut-off)		
Overall rate of severe AEs (CTCAE grade ≥ 3)[d] (until 9 December 2022)	31 (14.0)	38 (17.0)
Gastrointestinal disorders	9 (4.1)	23 (10.3)
Crohn's disease	3 (1.4)	11 (4.9)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC notation taken without adaptation from the data subsequently submitted by the company.
c. Including disease-related events.

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

Table 14: Discontinuation due to AEs[a] – RCT, direct comparison: risankizumab vs. ustekinumab

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Risankizumab N = 222**	**Ustekinumab N = 224**
SEQUENCE (12 January 2023 data cut-off)		
Overall rate of discontinuation due to AEs[b] (until 9 December 2022)	8 (3.6)	10 (4.5)
Gastrointestinal disorders	5 (2.3)	7 (3.1)
Abdominal pain	1 (0.5)	0 (0)
Ascites	0 (0)	1 (0.4)
Crohn's disease	3 (1.4)	6 (2.7)
Small intestinal perforation	1 (0.5)	0 (0)
Subileus	0 (0)	1 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.9)	0 (0)
Arthritis	1 (0.5)	0 (0)
Sacroiliitis	1 (0.5)	0 (0)
Reproductive system and breast disorders	0 (0)	1 (0.4)
Vaginal fistula	0 (0)	1 (0.4)
Skin and subcutaneous tissue disorders	1 (0.5)	2 (0.9)
Psoriasis	1 (0.5)	1 (0.4)
Urticaria	0 (0)	1 (0.4)

a. MedDRA version 25.0; SOC and PT notation taken without adaptation from the data subsequently submitted by the company.
b. Including disease-related events.

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