Mirikizumab (Crohn's disease)

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

EXTRACT

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Medical and scientific advice

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by Birgit Kaltz.

IQWiG thanks the respondent and the patient organization Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung (DCCV) e. V. for participating in the written exchange and for their support. The respondent and the DCCV were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
6-MP	6-mercaptopurine
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
AP	abdominal pain
AZA	azathioprine
CDAI	Crohn's Disease Activity Index
CRF	case report form
CSR	clinical study report
EMA	European Medicines Agency
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NRI	non-responder imputation
NRS	Numeric Rating Scale
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PGRS	Patient Global Rating of Severity
PRO2	patient-reported outcome 2
PT	Preferred Term
QIDS	Quick Inventory of Depressive Symptomatology
RCT	randomized controlled trial
SAE	serious adverse event
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency

Abbreviation	Meaning
SF-36	Short Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class
TNF	tumour necrosis factor
WPAI-CD	Work Productivity and Activity Impairment questionnaire – Crohn's Disease

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 mirikizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 10 March 2025.

Research question

The aim of this report is to assess the added benefit of mirikizumab in comparison with the appropriate comparator therapy (ACT) in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent (tumour necrosis factor [TNF]α antagonist or integrin inhibitor or interleukin inhibitor).

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of mirikizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy	Adalimumab or infliximab or risankizumab or ustekinumab or vedolizumab[b, c]
2	Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor)	Adalimumab or infliximab or risankizumab or upadacitinib or ustekinumab or vedolizumab[b, c]

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, a change of drug class can be considered as well as a change within the drug class. It is assumed that any possible dose adjustments have already been exhausted.
c. According to the G-BA, 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

If necessary for better readability, this benefit assessment uses the following terms for the patient populations of the research questions presented in Table 2:

- Research question 1: patients who are not eligible for conventional therapy
- Research question 2: patients who are not eligible for a biologic agent

In its dossier, the company referred to a consultation on 15 June 2022, without selecting any of the ACT options listed. The G-BA updated the ACT on 25 February 2025. The company deviated from this updated ACT of the G-BA for research question 2 by excluding upadacitinib. This had no consequences for this benefit assessment, as no study comparing mirikizumab versus upadacitinib was identified in the review of the completeness of the study pool in the context of this benefit assessment.

In this assessment, the added benefit was assessed in comparison with the updated ACT of the G-BA.

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

Study pool and study design

The VIVID-1 study was used for both research questions of the benefit assessment. This study is a double-blind, multicentre RCT comparing mirikizumab with ustekinumab or placebo in adults with moderately to severely active Crohn's disease who had an inadequate response to, loss of response to, or were intolerant to conventional therapy (with corticosteroids, azathioprine [AZA], 6-mercaptopurine [6-MP] or methotrexate [MTX]), a TNFα antagonist or an integrin inhibitor. The diagnosis must have been established at least 3 months before enrolment.

Disease severity and disease activity were defined using the following criteria at baseline:

- Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥ 7 for ileal-colonic disease, or SES-CD of ≥ 4 for isolated ileal disease, and
- An average daily stool frequency of ≥ 4 with liquid or very soft stools according to the Bristol Stool Scale type 6 or 7 (recorded using the Crohn's Disease Activity Index [CDAI] Stool Frequency scale [CDAI-SF]), and/or
- An average daily abdominal pain score ≥ 2 (recorded using the CDAI Abdominal Pain scale [CDAI-AP]; scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe pain)

The CDAI total score at baseline was not a criterion for defining severity in the VIVID-1 study. However, the values at baseline were mostly in a range concurring with moderate to severe disease activity. For this benefit assessment, it is assumed on the basis of the available information on the CDAI total score and other information on symptoms at baseline that most patients in the VIVID-1 study had moderately to severely active Crohn's disease.

To participate in the study, patients must have had an inadequate response to, lost response to, or shown intolerance to conventional therapy or a TNF antagonist (such as adalimumab or infliximab) or an integrin inhibitor (such as vedolizumab).

Non-eligibility for conventional therapy was defined based on the presence of one or more of the following criteria:

- Active disease after ≥ 4 weeks of corticosteroid treatment
- Corticosteroid-dependent disease (criteria used in the study concurred with the criteria of the current S3 guideline on the diagnosis and treatment of Crohn's disease)
- History of intolerance to corticosteroids
- Signs and/or symptoms of persistently active disease after ≥ 3 months of treatment with AZA, 6-MP or MTX
- Intolerance to AZA, 6-MP or MTX

Non-eligibility for a TNF antagonist or an integrin inhibitor was defined as an inadequate response despite induction treatment at the approved induction dosing, loss of response or intolerance.

A total of 1152 patients were included in the study and randomly assigned in a 6:3:2 ratio to treatment with mirikizumab (N = 631), ustekinumab (N = 309) or placebo (N = 212); the placebo arm is not relevant for this benefit assessment and is not discussed further. The study included relevant subpopulations for both research question 1 (non-eligibility for conventional therapy; 331 versus 164 patients) and research question 2 (non-eligibility for a biologic agent; 300 versus 145 patients) of this dossier assessment.

The treatment duration was 52 weeks or until disease worsening requiring treatment with specific drugs prohibited in the study or surgery, unacceptable toxicity, or treatment discontinuation by investigator decision or patient request.

Co-primary outcomes of the study were clinical response by patient-reported outcome 2 (PRO2) at Week 12 and endoscopic response at Week 25, as well as clinical response by PRO2 at Week 12 and clinical remission by CDAI at Week 52. Patient-relevant outcomes of morbidity, health-related quality of life and side effects were additionally recorded.

Relevant limitations of the VIVID-1 study

Comparator therapy not administered in full compliance with the SmPC

The VIVID-1 study used ustekinumab as comparator therapy. In the study, treatment with ustekinumab was induced with a weight-based single intravenous dose in compliance with the summary of product characteristics (SmPC). Eight weeks after the intravenous induction dose,

ustekinumab was administered subcutaneously every 8 weeks at a dose of 90 mg. However, the SmPC recommends treatment every 12 weeks after the first subcutaneous administration of 90 mg ustekinumab. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. In the VIVID-1 study, ustekinumab was therefore not administered fully in compliance with the SmPC. It is unclear to what extent this deviation influenced 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 VIVID-1 study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

Research question 1: patients who are not eligible for conventional therapy

Risk of bias and certainty of conclusions

The risk of bias was rated as high for the results for all outcomes except the outcome discontinuation due to adverse events (AEs).

For the outcomes on morbidity and health-related quality of life, for which suitable data were available, the high risk of bias was due to a high proportion of missing values at Week 52. It is possible that missing values were not adequately imputed.

For the outcomes serious adverse events (SAEs) and infections, the outcome-specific risk of bias was also rated as high. In each case, this was due to incomplete observations for potentially informative reasons. For the outcome SAEs, another reason for the high outcome-specific risk of bias was that high proportions of potentially disease-related events were included in the analyses presented.

For the outcome discontinuation due to AEs, there was a low risk of bias, but the certainty of the results for this outcome was limited because a high proportion of treatment discontinuations were due to reasons other than AEs.

Summary assessment of the certainty of conclusions

Based on the VIVID-1 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

Results

Mortality

All-cause mortality

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

Morbidity

Corticosteroid-free clinical remission (PRO2), bowel symptoms (IBDQ), systemic symptoms (IBDQ), bowel urgency remission (Urgency NRS), fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcomes corticosteroid-free clinical remission (recorded using PRO2), bowel symptoms and systemic symptoms (each recorded using the Inflammatory Bowel Disease Questionnaire [IBDQ]), bowel urgency remission (recorded using Urgency NRS), fatigue (recorded using FACIT-Fatigue) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Extraintestinal manifestations, fistulae and activity impairment (WPAI-CD Item 6)

No suitable data were available for any of the outcomes extraintestinal manifestations, fistulae and activity impairment (recorded using Work Productivity and Activity Impairment questionnaire – Crohn's Disease [WPAI-CD] Item 6). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score, SF-36 Physical Component Summary (PCS) and SF-36 Mental Component Summary (MCS)

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using IBDQ and SF-36). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs and infections (AEs)

There was no statistically significant difference between the treatment groups for any of the outcomes SAEs, discontinuation due to AEs and infections (AEs). There was no hint of greater

or lesser harm from mirikizumab in comparison with ustekinumab for any of the outcomes; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3] (research question 1: patients who are not eligible for conventional therapy)

Based on the results presented, probability and extent of the added benefit of the drug mirikizumab in comparison with the ACT are assessed as follows:

For research question 1 of this benefit assessment, neither positive nor negative effects of mirikizumab compared with ustekinumab were shown in the relevant subpopulation. In summary, there is no hint of an added benefit of mirikizumab versus the ACT for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy. An added benefit is therefore not proven.

Research question 2: patients who are not eligible for a biologic agent

Risk of bias and certainty of conclusions

The outcome-specific risk of bias did not differ between research question 1 and research question 2. Based on the VIVID-1 study, at most hints, e.g. of an added benefit, could therefore be derived for all outcomes presented, also for research question 2.

Results

Due to the clearly uneven distribution of patients included in the study within versus outside of Europe between the research questions, the results of the subgroup analyses on the characteristic of geographical region were additionally considered as part of this assessment. For research question 2, these showed numerous significant effect modifications that affected almost all key outcomes. Significant advantages were only shown in the region 'other', which included approximately 80% of patients in Asia. This was taken into account in the derivation of the added benefit for research question 2.

[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].

Mortality

All-cause mortality

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

Morbidity

Corticosteroid-free clinical remission (PRO2), bowel symptoms (IBDQ), fatigue (FACIT-Fatigue), health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcomes corticosteroid-free clinical remission (recorded using PRO2), bowel symptoms (recorded using IBDQ), fatigue (recorded using FACIT-Fatigue) and health status (recorded using EQ-5D VAS). In each case, there was no hint of an added benefit of mirikizumab in comparison with the ACT; an added benefit is therefore not proven.

Extraintestinal manifestations, fistulae and activity impairment (WPAI-CD Item 6)

No suitable data were available for any of the outcomes extraintestinal manifestations, fistulae and activity impairment (recorded using Work Productivity and Activity Impairment questionnaire – Crohn's Disease [WPAI-CD] Item 6). In each case, there was no hint of an added benefit of mirikizumab in comparison with the ACT; an added benefit is therefore not proven.

Bowel urgency remission (Urgency NRS)

There was a statistically significant difference in favour of mirikizumab in comparison with ustekinumab for the outcome bowel urgency remission (recorded using Urgency NRS). However, the extent of the effect for this outcome in the category of non-serious/non-severe symptoms was no more than marginal. There was no hint of an added benefit of mirikizumab in comparison with the ACT; an added benefit is therefore not proven.

Systemic symptoms (IBDQ)

There was no statistically significant difference between the treatment groups for the outcome systemic symptoms (recorded using the IBDQ). However, there was an effect modification by the characteristic of CDAI total score at baseline. For patients with a CDAI total score < 300 at baseline, there was a hint of an added benefit of mirikizumab compared with the ACT. For patients with a CDAI total score ≥ 300 at baseline, there was no hint of an added benefit of mirikizumab compared with the ACT; an added benefit is therefore not proven for patients with a CDAI total score ≥ 300 at baseline.

Health-related quality of life

IBDQ total score, SF-36 PCS and SF-36 MCS

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using IBDQ and SF-36). In each case, there was no hint of an added benefit of mirikizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes of SAEs or discontinuation due to AEs. There was no hint of greater or lesser harm from mirikizumab in comparison with the ACT for either of the outcomes; greater or lesser harm is therefore not proven.

Infections (AEs)

There was a statistically significant difference in favour of mirikizumab in comparison with ustekinumab for the outcome infections (AEs). However, the extent of the effect for this outcome in the category of non-serious/non-severe side effects was no more than marginal. There was no hint of greater or lesser harm from mirikizumab in comparison with the ACT; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit (research question 2: patients who are not eligible for a biologic agent)

Based on the results presented, probability and extent of the added benefit of the drug mirikizumab in comparison with the ACT are assessed as follows:

For research question 2 of this benefit assessment, only one positive effect was shown in the relevant subpopulation for patients with a CDAI total score < 300 at baseline. This positive effect concerned the outcome systemic symptoms (IBDQ – improvement) and represented a hint of minor added benefit. In the overall assessment of the available results and taking into account the results of the subgroup analyses for the characteristic of geographical region, this positive effect in one subgroup was not sufficient to derive an added benefit of mirikizumab in the overall assessment.

In summary, there is no hint of an added benefit of mirikizumab versus the ACT for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor). An added benefit is therefore not proven.

Probability and extent of added benefit – summary

Table 3 presents a summary of the probability and extent of the added benefit of mirikizumab in comparison with the ACT.

Table 3: Mirikizumab – probability and extent of the added benefit

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

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, a change of drug class can be considered as well as a change within the drug class. It is assumed that any possible dose adjustments have already been exhausted.
c. According to the G-BA, continuation of an inadequate therapy does not concur with the specified ACT.
d. The VIVID-1 study did not include any patients who had received risankizumab as prior therapy or who had an inadequate response with, lost response to, or were intolerant to ustekinumab as prior therapy. It remains unclear whether the observed effects can be transferred to the corresponding patients.

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

The approach for the derivation of 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 mirikizumab in comparison with the ACT in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor).

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of mirikizumab

Research question	Therapeutic indication	ACT[a]
1	Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy	Adalimumab or infliximab or risankizumab or ustekinumab or vedolizumab[b, c]
2	Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor)	Adalimumab or infliximab or risankizumab or upadacitinib or ustekinumab or vedolizumab[b, c]

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, a change of drug class can be considered as well as a change within the drug class. It is assumed that any possible dose adjustments have already been exhausted.
c. According to the G-BA, 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

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

- Research question 1: patients who are not eligible for conventional therapy
- Research question 2: patients who are not eligible for a biologic agent

In its dossier, the company referred to a consultation on 15 June 2022 [3], without selecting any of the ACT options listed. The G-BA updated the ACT on 25 February 2025. In this assessment, the added benefit was assessed in comparison with the updated ACT of the G-BA presented in Table 4 [4].

For research question 1, the company named a TNFα antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab or risankizumab) as the ACT, and thus followed the updated specification of the G-BA for this research question.

For research question 2, the company named a treatment switch to a TNFα antagonist (adalimumab or infliximab) or integrin inhibitors (vedolizumab) or interleukin inhibitors (ustekinumab or risankizumab) as the ACT, and thus deviated from the updated specification of the G-BA by excluding upadacitinib. This had no consequences for this benefit assessment, as no study comparing mirikizumab versus upadacitinib was identified in the review of the completeness of the study pool in the context of this benefit assessment (see Chapter I 3).

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on mirikizumab (status: 18 December 2024)
- Bibliographical literature search on mirikizumab (last search on 18 December 2024)
- Search of trial registries/trial results databases for studies on mirikizumab (last search on 18 December 2024)
- Search on the G-BA website for mirikizumab (last search on 10 January 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on mirikizumab (last search on 27 March 2025); for search strategies, see I Appendix A of the full benefit assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: mirikizumab vs. ACT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
VIVID-1	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8]

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

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial

The VIVID-1 study comparing mirikizumab with ustekinumab was used for the benefit assessment. The study pool was consistent with that selected by the company.

I 3.2 Study characteristics (aspects across research questions)

As the included study VIVID-1 was relevant for both research questions of this benefit assessment, characteristics across research questions are described below. Research

question-specific characteristics for research question 1 are described in Section I 4.1, and those for research question 2 are described in Section I 5.1.

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]
VIVID-1	RCT, double-blind, parallel	Adult patients (≤ 80 years) with moderately to severely active Crohn's disease[b, c] and ▪ SES-CD total score[d] ▫ ≥ 7 for ileal-colonic disease or ▫ ≥ 4 for isolated ileal disease ▪ Confirmed inadequate response, loss of response, or intolerance ▫ to conventional therapies (corticosteroids[e, f] or immunosuppressants[g, f]) and no failure / no intolerance to TNFα antagonists or integrin inhibitors or ▫ to TNFα antagonists or integrin inhibitors[h, f]	Mirikizumab (N = 631) Ustekinumab (N = 309) Placebo (N = 212)[i] Relevant subpopulations thereof: ▪ Subpopulation A[j] mirikizumab (n = 331) ustekinumab (n = 164) ▪ Subpopulation B[k] mirikizumab (n = 300) ustekinumab (n = 145)	Screening: up to 5 weeks Treatment: 52 weeks or until occurrence of ▪ disease worsening requiring specific drugs prohibited in the study or surgery ▪ unacceptable toxicity or ▪ treatment discontinuation at investigator or patient decision Observation: up to a maximum of 16 weeks after the end of treatment	328 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, France, Germany, Hungary, India, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Poland, Romania, Russia, Serbia, Slovakia, South Korea, Spain, Switzerland, Turkey, Ukraine, United Kingdom, United States 7/2019–8/2023 Data cut-off: 4 October 2023[l]	Primary: ▪ Clinical and endoscopic response ▪ Clinical response and clinical remission Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Moderately to severely active Crohn's disease in the VIVID-1 study is defined by unweighted daily average stool frequency ≥ 4 (liquid or very soft stools according to the Bristol Stool Scale type 6 or 7) and/or unweighted daily average abdominal pain ≥ 2 (scale from 0 = none to 3 = severe) at baseline.
c. The diagnosis had to be confirmed by clinical, endoscopic and histologic criteria ≥ 3 months prior to enrolment.
d. Centrally recorded ≤ 21 days prior to randomization.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study implementation	Primary outcome; secondary outcomes[a]
e. Criteria for the failure of corticosteroids: ▫ Corticosteroid-refractory disease, defined as signs and/or symptoms of active Crohn's disease despite ≥ 4 weeks of oral prednisone (or equivalent) ≥ 30 mg/day, or budesonide ≥ 9 mg/day. ▫ Corticosteroid-dependent disease, defined as an inability to reduce corticosteroids below the equivalent of prednisone 10 mg/day or budesonide below 3 mg/day within 3 months of starting treatment without a return of signs and/or symptoms of active Crohn's disease, or a relapse within 3 months of completing corticosteroid treatment. History of intolerance to corticosteroids (which includes side effects sufficiently serious as to precluding continued treatment, including Cushing's syndrome, osteopenia/osteoporosis, hyperglycaemia, or neuropsychiatric side effects, including insomnia associated with corticosteroid treatment). f. Discontinuation of treatment despite clinical benefit is not considered failure or intolerance to therapy. g. Criteria for the failure of immunosuppressants: ▫ Signs and/or symptoms of persistently active disease despite at least 3 months' treatment with one of the following drugs: oral AZA (≥ 1.5 mg/kg/day) or 6-MP (≥ 0.75 mg/kg/day) or MTX (25 mg/weekly, intramuscular or SC) or oral AZA or 6-MP or a combination of a thiopurine and allopurinol within a therapeutic range as judged by thioguanine metabolite testing History of intolerance to ≥ 1 immunosuppressant (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities and lymphopenia). h. One of the following criteria should be fulfilled: inadequate response to therapy: signs and symptoms of persistently active disease despite induction treatment at the approved induction dosing (according to the SmPC), or loss of response: recurrence of signs and symptoms of active disease following prior clinical benefit during treatment with approved maintenance dosing, or intolerance: history of intolerance to infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab or other approved biologics (including but not limited to infusion-related event, demyelination, congestive heart failure, or any other drug-related AE that led to a reduction in dose or discontinuation of the medication). i. The arm is irrelevant for the assessment and is disregarded in the following tables. j. Patients for whom conventional therapy is unsuitable. k. Patients for whom a biologic agent was unsuitable (e.g. TNFα antagonist or integrin inhibitor); patients who were not eligible for an IL-23p19 inhibitor such as risankizumab, or an IL-12/23p40 inhibitor such as ustekinumab, were excluded from the study. l. Prespecified final analysis for the primary outcomes after 52 weeks of treatment of all patients. 6-MP: 6-mercaptopurine; AE: adverse event; AZA: azathioprine; 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: mirikizumab vs. ustekinumab (multipage table)

Study	Intervention	Comparison
VIVID-1	Mirikizumab ▪ Weeks 0–12: 900 mg, IV, every 4 weeks ▪ Weeks 12–52: 300 mg, SC, every 4 weeks	Ustekinumab ▪ Weeks 0–12: first dose: 6 mg/kg, IV, after 8 weeks: 90 mg, SC ▪ Weeks 12–52: 90 mg, SC, every 8 weeks
	Dose adjustments: not allowed	
	Required pretreatment ▪ ≥ 1 of the following therapies (with the restrictions specified below) ▫ Conventional therapies: corticosteroids, immunosuppressants or ▫ Biologics approved for Crohn's disease, e.g. TNFα antagonist or integrin inhibitor **Prohibited prior and concomitant treatment** ▪ Anti-IL-23p19 antibodies (e.g. risankizumab, brazikumab, guselkumab or tildrakizumab) ▪ Agents depleting B or T cells (e.g. rituximab, alemtuzumab or visilizumab) ≤ 12 months prior to baseline[a] ▪ Bowel resection ≤ 6 months prior to baseline[a] or intra-abdominal surgery ≤ 3 months prior to baseline[a] ▪ Natalizumab ≤ 12 months[b] prior to screening endoscopy ▪ ≤ 8 weeks prior to screening endoscopy: ▫ Investigational biological products[b, c] ▫ Interferon ▪ ≤ 4 weeks prior to screening endoscopy: ▫ Immunomodulators, including cyclosporine (oral and IV), tacrolimus, mycophenolate mofetil, thalidomide or Janus kinase inhibitors ▫ TNFα antagonists (e.g. infliximab, adalimumab or certolizumab pegol) ▫ Other integrin inhibitors (e.g. vedolizumab) ▫ Investigational non-biological products[d] ▪ ≤ 3 weeks prior to screening endoscopy: leukocyte apheresis ▪ ≤ 2 weeks prior to screening endoscopy: ▫ Corticosteroids (rectal or IV[e]) ▫ 5-ASA (rectal) **Allowed concomitant treatment** ▪ Oral 5-ASA (e.g. mesalamine, balsalazide or olsalazine)[f] ▪ Immunosuppressants (e.g. AZA, 6-mercaptopurine or methotrexate)[g] ▪ Oral corticosteroids (prednisone ≤ 30 mg/day or equivalent or budesonide 9 mg/day)[h] ▪ Corticosteroids for local use ▪ Antibiotics used specifically for Crohn's disease (e.g. rifaximin and ciprofloxacin)[i] ▪ Antidiarrhoeal drugs (e.g. loperamide or diphenoxylate with atropine) ▪ Low-dose aspirin (75–162.2 mg) for daily cardiovascular prophylaxis	

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

Study	Intervention	Comparison
a. Baseline means Visit 2 (= start of study medication). b. Discrepant information within Module 4 A; it is assumed that the information according to the study protocol is correct. c. ≤ 8 weeks prior to the screening endoscopy or ≤ 5 half-lives, whichever is longer. d. ≤ 4 weeks prior to the screening endoscopy or ≤ 5 half-lives, whichever is longer. e. IV corticosteroids were only permitted during the study as premedication for an infusion or for short-term treatment of acute events unrelated to Crohn's disease. f. At a stable dose for ≥ 2 weeks prior to the screening endoscopy. g. At a stable dose for ≥ 8 weeks prior to the screening endoscopy. h. Unchanged up to Week 12 at a stable dose for ≥ 2 weeks prior to the screening endoscopy; from Week 12 onwards, all patients on corticosteroid therapy who achieved clinical response tapered corticosteroids according to the following schedule: For initial dose > 10 mg/day prednisone equivalent, taper daily dose by 5 mg/week until 10 mg/day, then continue tapering at 2.5 mg/week until 0 g/day; for initial dose ≤ 10 mg/day prednisone equivalent, taper daily dose by 2.5 mg/week until 0 mg/day; for patients receiving budesonide, taper daily dose by 3 mg every 3 weeks to 0 mg/day. If clinical symptoms recur during the taper, tapering can be interrupted and/or the dose can be increased again to a maximum of the level at baseline. In these cases, tapering should be continued within 2 weeks and, if possible, completed by Week 40. i. At a stable dose since 4 weeks prior to baseline. 5-ASA: 5-aminosalicylic acid; AZA: azathioprine; IL-23p19: interleukin-23, p19 subunit; IV: intravenous; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor		

The VIVID-1 study is a double-blind, multicentre RCT comparing mirikizumab with ustekinumab or placebo in adults with moderately to severely active Crohn's disease who had an inadequate response to, loss of response to, or were intolerant to conventional therapy (with corticosteroids, AZA, 6-MP or MTX), a TNFα antagonist or an integrin inhibitor. The initial diagnosis of Crohn's disease must have been established at least 3 months before enrolment.

Disease severity and disease activity were defined using the following criteria at baseline:

- Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥ 7 for ileal-colonic disease, or SES-CD of ≥ 4 for isolated ileal disease, and
- An average daily stool frequency of ≥ 4 with liquid or very soft stools according to the Bristol Stool Scale type 6 or 7 (recorded using the CDAI-SF), and/or
- An average daily abdominal pain score ≥ 2 (recorded using the CDAI-AP; scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe pain)

The CDAI score at baseline was not a criterion for defining severity in the VIVID-1 study. However, the values at baseline were predominantly ≥ 220 (research question 1: 90% versus 85%, research question 2: 90% versus 92% [Institute's calculation]; see also Table 8 and Table 16), which concurs with moderate to severe disease activity [9]. For this benefit

assessment, it is assumed on the basis of the available information on the CDAI score and other information on symptoms at baseline that most patients in the VIVID-1 study had moderately to severely active Crohn's disease.

To participate in the study, patients must have had an inadequate response to, lost response to, or shown intolerance to conventional therapy or a TNF antagonist (such as adalimumab or infliximab) or an integrin inhibitor (such as vedolizumab).

Non-eligibility for conventional therapy was defined based on the presence of one or more of the following criteria:

- Active disease after ≥ 4 weeks of corticosteroid treatment
- Corticosteroid-dependent disease (criteria used in the study concurred with the criteria of the current S3 guideline on the diagnosis and treatment of Crohn's disease [10])
- History of intolerance to corticosteroids
- Signs and/or symptoms of persistently active disease after ≥ 3 months of treatment with AZA, 6-MP or MTX
- Intolerance to AZA, 6-MP or MTX

Non-eligibility for a TNF antagonist or an integrin inhibitor was defined as an inadequate response despite induction treatment at the approved induction dosing, loss of response or intolerance.

The following patients were excluded from the study: patients who had received prior therapy with an interleukin (IL)-23p19 inhibitor (such as risankizumab) or who had discontinued prior therapy with an IL-12/23p40 inhibitor (such as ustekinumab) due to inadequate response, loss of response or intolerance, or who had received more than the intravenous induction dose and a subcutaneous dose.

Patients with a current diagnosis of ulcerative colitis or indeterminate chronic inflammatory bowel disease were excluded from the study. Furthermore, they were not allowed to have any manifestations that could have required surgery within 6 months after screening. Patients who had been treated with stable doses of corticosteroids for at least 2 weeks prior to the screening endoscopy were eligible to participate in the study (see Table 7 for details on dosing and the tapering regimen for corticosteroids after randomization).

A total of 1152 patients were included in the study and randomly assigned in a 6:3:2 ratio to treatment with mirikizumab (N = 631), ustekinumab (N = 309) or placebo (N = 212); the placebo arm is not relevant for this benefit assessment and is not discussed further. Randomization was stratified by prior therapy (non-eligibility for a biologic agent: yes versus

no), corticosteroid use at baseline (yes versus no), baseline SES-CD total score (< 12 versus ≥ 12), region (North America versus Europe versus other) and either baseline CDAI-SF ≥ 7 and/or baseline CDAI-AP ≥ 2.5 (yes versus no). The stratification factor non-eligibility for a biologic agent concurs with the subdivision into the relevant subpopulations for research question 1 (no: non-eligibility for conventional therapy; 331 versus 164 patients) and research question 2 (yes: non-eligibility for a biologic agent; 300 versus 145 patients) of this dossier assessment.

Initiating corticosteroid therapy as concomitant treatment was generally permitted during the study (prednisone ≤ 30 mg/day or equivalent or budesonide 9 mg/day), while pre-existing corticosteroid therapy at a stable dose for at least 2 weeks prior to baseline was to be continued, if possible at a stable dose, up to Week 12. From Week 12, patients who were receiving corticosteroids and who achieved clinical response had to taper their corticosteroid dose following a specified schedule (see Table 7 for details).

The treatment duration was 52 weeks or until disease worsening requiring treatment with specific drugs prohibited in the study or surgery, unacceptable toxicity, or treatment discontinuation by investigator decision or patient request.

Co-primary outcomes of the study were clinical response by PRO2 at Week 12 and endoscopic response at Week 25, as well as clinical response by PRO2 at Week 12 and clinical remission by CDAI at Week 52. Patient-relevant outcomes of morbidity, health-related quality of life and side effects were additionally recorded.

Limitations of the VIVID-1 study

The results of the VIVID-1 study were used for the benefit assessment. However, there were limitations, which are described below.

Lack of specification of treatment discontinuation due to lack of efficacy

According to the SmPC of mirikizumab, consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by Week 24 [11]. Analogously, according to the SmPC of ustekinumab, consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the intravenous induction dose or 16 weeks after switching to the maintenance dose [12,13]. In the RCT VIVID-1, it was generally possible to discontinue treatment with mirikizumab or ustekinumab due to a lack of efficacy. However, a recording of the clinical benefit at a relevant point in time and the associated decision on the further course of treatment were not planned. It therefore remains unclear whether all patients in the study received their treatment in compliance with the SmPC recommendations. At Week 24, in the total population of the VIVID-1 study, 17.1% versus 17.9% (Institute's calculation) of the patients still under observation at this time point had not achieved a clinical response

(recorded using PRO2). No data on clinical response were available for the subpopulations relevant for the assessment concurring with the research questions of this dossier assessment, not even at other time points. The proportion of patients without clinical response at Week 24 was roughly balanced in both study arms. In the given data situation, it was not assumed that this deviation from the recommendations in the SmPC had a substantial effect on the results.

Comparator therapy not administered in full compliance with the SmPC

The VIVID-1 study used ustekinumab as comparator therapy. In the study, treatment with ustekinumab was induced with a weight-based single intravenous dose in compliance with the SmPC [14]. Eight weeks after the intravenous induction dose, ustekinumab was administered subcutaneously every 8 weeks at a dose of 90 mg. However, the SmPC [12,13] recommends dosing every 12 weeks after the first subcutaneous administration of 90 mg ustekinumab. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. In the VIVID-1 study, ustekinumab was therefore not administered fully in compliance with the SmPC. It is unclear to what extent this deviation influenced the effects of the patient-relevant outcomes observed in the study. This uncertainty was taken into account when assessing the certainty of conclusions (see Section I 4.2.2).

In summary, on the basis of the effects shown in the VIVID-1 study, at most hints, e.g. of an added benefit, can therefore be derived for all outcomes.

Ustekinumab not approved for non-eligibility for integrin inhibitors

Patients who had responded inadequately to, lost response to, or demonstrated an intolerance to an integrin inhibitor were also eligible for participating in the VIVID-1 study. However, according to the SmPC, this is not a suitable criterion for the use of ustekinumab [12-14]. With regard to pretreatment, the SmPC only mentions conventional therapy and TNF antagonists, but not integrin inhibitors [12-14]. However, this was not considered a relevant limitation of the study, as according to Module 4 A, a TNF inhibitor was not suitable for 96% of patients in the comparator arm of the relevant subpopulation, thus providing sufficient grounds for the on-label use of ustekinumab (see Table 16).

Discontinuation of prior therapy with a biologic agent without treatment failure

The VIVID-1 study subpopulation relevant to research question 1 also included patients who had received prior therapy with a biologic agent without treatment failure. It was unclear why treatment with the respective biologic agent was discontinued in these patients and whether there was a therapeutic indication for switching treatment. Since the proportion of patients affected was small (11% versus 7%) and was similar in both arms (see Table 8), this was of no consequence for this benefit assessment.

I 4 Research question 1: patients who are not eligible for conventional therapy

I 4.1 Study characteristics (specific to research question 1)

For characteristics of the VIVID-1 study that apply to all research questions, see Section I 3.2.

I 4.1.1 Patient characteristics

Table 8 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 1.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) (multipage table)

Study **Characteristic** **Category**	**Mirikizumab** **N = 331**	**Ustekinumab** **N = 164**
VIVID-1		
Age [years], mean (SD)	37 (13)	37 (13)
Sex [F/M], %	46/54	49/51
Region, n (%)		
Europe	224 (68[a])	121 (74[a])
North America	31 (9)	13 (8)
Other	76 (23[a])	30 (18[a])
Asia	58 (18)	23 (14)
Central or South America	11 (3)	7 (4)
Australia	7 (2)[a]	0 (0)[a]
Time since diagnosis of Crohn's disease [months], mean (SD)	6.1 (8.0)	5.2 (5.9)
Disease location, n (%)		
Colon isolated	135 (41)	73 (45)
Ileum isolated	41 (12)	24 (15)
Ileocolon	155 (47)	65 (40)
SES-CD total score at baseline, mean (SD)	12.0 (6.5)	12.2 (6.5)
CDAI total score at baseline		
Mean (SD)	314.8 (80.3)	313.4 (88.3)
< 150, n (%)	5 (2[a])	6 (4[a])
≥ 150 to < 220, n (%)	27 (8[a])	18 (11[a])
≥ 220 to < 450, n (%)	275 (83[a])	125 (76[a])
≥ 450, n (%)	23 (7[a])	15 (9[a])

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) (multipage table)

Study **Characteristic** **Category**	**Mirikizumab** **N = 331**	**Ustekinumab** **N = 164**
Average stool frequency (CDAI-SF) at baseline, mean (SD)	5.4 (2.5)	5.5 (2.5)
Average abdominal pain (CDAI-AP) at baseline, mean (SD)	2.1 (0.6)	2.1 (0.6)
Average bowel urgency (Urgency NRS) at baseline, mean (SD)	6.5 (2.1)	6.6 (2.0)
IBDQ total score at baseline, mean (SD)	128.0 (33.2)	123.7 (35.2)
IBDQ bowel symptoms at baseline, mean (SD)	38.2 (9.7)	37.3 (10.4)
IBDQ systemic symptoms at baseline, mean (SD)	18.0 (5.8)	17.4 (5.9)
SF-36 at baseline, mean (SD)		
Physical Component Summary (PCS)	40.0 (7.3)	40.0 (8.0)
Mental Component Summary (MCS)	43.4 (10.9)	42.3 (10.8)
Failure of prior therapy, n (%)		
Prior corticosteroid failure	216 (65)	126 (77)
Prior immunosuppressant failure	180 (54)	77 (47)
Prior therapy with a biologic agent without treatment failure	36 (11)	12 (7)
Treatment discontinuation in the double-blind phase, n (%)[b]	47 (14)	21 (13)
Study discontinuation, n (%)	ND	ND

a. Institute's calculation.
b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were the following (percentages based on randomized patients): patient decision (4% vs. 5%) and AEs (6% vs. 2%). The therapy in the double-blind phase was completed as planned by 284 vs. 143 of the patients.

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; ND: no data; NRS: numeric rating scale; 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

The baseline patient characteristics for the relevant subpopulation in the VIVID-1 study were sufficiently comparable between the 2 treatment arms. The mean age of the patients was 37 years, and only a small proportion (2.7% versus 2.4%) were ≥ 65 years of age. Around 68% versus 74% came from the region of Europe, which means that the geographical distribution of this subpopulation differed greatly from the subpopulation relevant for research question 2 (see Section I 5.1.1). The mean of the daily average stool frequency (by CDAI-SF) was just over 5 and the abdominal pain (by CDAI-AP) was approximately 2 (ranging from 0 = no pain to 3 = severe pain). The CDAI total score was in the range of ≥ 220 to < 450 in around 80% of patients. Prior therapy with corticosteroids had failed in 65% versus 77% of the patients, and treatment with immunosuppressants had failed in 54% versus 47%. As already described in

Section I 3.2, a small proportion of patients had received prior therapy with a biologic agent without treatment failure.

The proportion of patients with treatment discontinuation was balanced at around 14% in both study arms; the most common reasons for treatment discontinuation were patient request or AEs. No data were available on the proportion of patients with study discontinuation.

I 4.1.2 Concomitant treatments

Concomitant treatments with corticosteroids and/or immunosuppressants at baseline or during the course of the study are shown in Table 9.

Table 9: Information on concomitant treatments with corticosteroids and/or immunosuppressants – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy)

Study **Time point** **Drug class**	**Patients with concomitant treatment, n (%)**	
	Mirikizumab **N = 331**	**Ustekinumab** **N = 164**
VIVID-1		
Concomitant treatments at baseline		
Corticosteroids[a]	113 (34.1)[b]	56 (34.1)[b]
Immunosuppressants[c]	102 (30.8)[b]	53 (32.3)[b]
Corticosteroids[a] and immunosuppressants[c]	23 (6.9)	12 (7.3)
Neither corticosteroids[a] nor immunosuppressants[c]	139 (42.0)	67 (40.9)
Concomitant treatments during the study		
Corticosteroids[a]	129 (39.0)[b]	65 (39.6)[b]
Locally effective corticosteroids	54 (16.3)	29 (17.7)
Budesonide	54 (16.3)	28 (17.1)
Prednisolone	0 (0)	1 (0.6)
Immunosuppressants[c]	103 (31.1)[b]	55 (33.5)[b]
Corticosteroids[a] and immunosuppressants[c]	28 (8.5)	18 (11.0)
Neither corticosteroids[a] nor immunosuppressants[c]	127 (38.4)	62 (37.8)

a. Locally administered corticosteroids (e.g. inhaled, intranasal, intra-articular or topical) that were not used for the treatment of Crohn's disease were not included in the calculation.
b. Institute's calculation.
c. For example azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (MTX).

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

The proportion of patients receiving concomitant therapy with corticosteroids and/or immunosuppressants at baseline was balanced between the study arms. The frequency with

which concomitant therapies were used during the study was also about equal in both study arms, with around 39% of patients in both arms receiving treatment with corticosteroids during the study.

I 4.1.3 Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: mirikizumab vs. ustekinumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
VIVID-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the VIVID-1 study.

I 4.1.4 Transferability of the study results to the German health care context

The company explained that the relevant characteristics of the patient populations investigated in the VIVID-1 study were comparable to the general characteristics of patients covered by the therapeutic indication of mirikizumab in Germany. According to the company, the results of the VIVID-1 study were therefore transferable to the German health care context. It also considered the dosing regimen for ustekinumab and the regimen for corticosteroid tapering in the VIVID-1 study to be transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also Section I 5.2.4.

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

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

- Mortality

- All-cause mortality

- Morbidity
  - Corticosteroid-free clinical remission, recorded using PRO2
  - Bowel symptoms, recorded using the IBDQ subscore of bowel symptoms
  - Systemic symptoms, recorded using the IBDQ subscore of systemic symptoms
  - Bowel urgency remission, recorded using the Urgency NRS
  - Extraintestinal manifestations
  - Fistulae
  - Fatigue, recorded using the FACIT-Fatigue
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
  - Activity impairment, recorded using the WPAI-CD Item 6
- Health-related quality of life
  - recorded using the IBDQ and the SF-36
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Infections, operationalized as infections and infestations (System Organ Class [SOC], AEs)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4).

Table 11 shows for which outcomes data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: mirikizumab vs. ustekinumab

Study	Outcomes													
	All-cause mortality[a]	Corticosteroid-free clinical remission (PRO2)	Bowel symptoms, systemic symptoms (IBDQ)	Bowel urgency remission (Urgency NRS)	Extraintestinal manifestations	Fistulae	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Activity impairment (WPAI-CD Item 6)	Health-related quality of life (IBDQ, SF-36)	SAEs	Discontinuation due to AEs	Infections[b]	Other specific AEs
VIVID-1	Yes	Yes	Yes	Yes	No[c]	No[c]	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	No[d]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as infections and infestations (SOC, AEs).
c. No suitable data available; for the reasoning, see Section I 4.2.1 of this dossier assessment.
d. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; FACIT: Functional Assessment of Chronic Illness Therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; NRS: numeric rating scale; PRO2: patient-reported outcome 2 (abdominal pain and stool frequency); RCT: randomized controlled trial; SAE: serious adverse event; SF: stool frequency; SF-36: Short Form 36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

Outcomes on morbidity and health-related quality of life

Clinical remission (PRO2) and corticosteroid-free clinical remission (PRO2)

In Module 4, the company presented 2 outcomes on remission: clinical remission and corticosteroid-free clinical remission. Both outcomes were operationalized using PRO2. The PRO2 comprises the 2 scales of the CDAI on stool frequency (CDAI-SF) and on abdominal pain (CDAI-AP; on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe pain), each of which were recorded using a patient diary. According to the predefinition in the study design, remission by PRO2 was defined as an unweighted daily average stool frequency (CDAI-SF) ≤ 3 and unweighted daily average abdominal pain (CDAI-AP) ≤ 1 (each averaged over a period of 7 days) at Week 52, with both values no worse than baseline. According to the company's information in Module 4 A, the patient relevance of these predefined response criteria was supported by psychometric evaluations in patients with moderate to severe Crohn's disease [15]. The operationalization of clinical remission based on these criteria corresponded to a largely symptom-free condition of the patients and was therefore face valid. Corticosteroid-free clinical remission was operationalized as clinical remission by PRO2 at Week 52 and corticosteroid-free treatment between Week 40 and Week 52.

It should be noted that individual values for calculating the daily average might have been missing for patients with available data at Week 52. The study protocol of the VIVID-1 study showed that the 7 most recent values from the patient diary within the 12-day period prior to a visit were used to calculate the daily average. If 4 to 7 values were available, these values were used and any missing values were not imputed. If fewer than 4 values were available, the daily average was not calculated and reported as missing. It is unclear for how many patients values for individual days were missing. This led to additional uncertainty for this outcome, which went beyond the uncertainty described in the section on the risk of bias due to the high proportion of missing values (see Section I 4.2.2).

According to the study design, the outcome corticosteroid-free clinical remission by CDAI was predefined. However, the operationalization of remission by CDAI was not suitable for the assessment: On the one hand, the CDAI not only includes the patient-relevant components contained in PRO2 (stool frequency and abdominal pain, see below), but also parameters that do not represent changes that are directly noticeable for patients (e.g. investigations: haematocrit, body weight). Secondly, the company did not provide any information on the validity of the CDAI in the target population under investigation. The European Medicines Agency (EMA) also advises against using the CDAI as an outcome in the therapeutic indication of Crohn's disease [16]. Against this background, the operationalization of corticosteroid-free clinical remission by PRO2 presented in Module 4 was considered adequate. The outcome corticosteroid-free clinical remission by PRO2 was used in this assessment. This is justified below.

The current S3 guideline describes corticosteroid-free remission (i.e. without the use of systemic corticosteroids or oral budesonide) as an important treatment goal [10]. Achieving corticosteroid-free clinical remission was considered patient relevant in this benefit assessment. According to current guidelines, systemic corticosteroids should generally not be used for remission maintenance due to serious side effects in long-term therapy, and their use should be minimized in clinical practice [10,17]. Achieving remission whilst remaining free of systemic corticosteroids is therefore also a patient-relevant outcome from the perspective of avoiding long-term side effects. Corticosteroid-free remission was also considered a more sustainable definition of remission: The outcome clinical remission (PRO2) also included patients as responders who achieved remission with corticosteroids or at least maintained remission between Week 40 and Week 52. It was assumed that achieving clinical remission without the use of corticosteroids or by adhering to the 3-month waiting period represented a more stable therapeutic effect. Based on the dose reduction scheme used in the VIVID-1 study to taper corticosteroids (see Section I 3.2), it was assumed that corticosteroid-free clinical remission was generally achievable for most patients in the VIVID-1 study. The high proportion of patients who achieved a corticosteroid-free clinical remission at Week 52 (see Sections I 4.2.3 and I 5.2.3) also suggested that this was an achievable outcome in the

therapeutic indication. The results for the outcome clinical remission (PRO2) are presented as supplementary information.

The predefined 3-month period of corticosteroid-free treatment as a prerequisite for corticosteroid-free remission was considered adequate: If the disease relapses within 3 months of discontinuing corticosteroids, the disease is assumed to be corticosteroid-dependent according to current guidelines [10,17]. When operationalizing corticosteroid-free treatment, a distinction must also be made between locally and systemically active corticosteroids and their possible local or systemic side effects. In the VIVID-1 study, however, only a small proportion of patients received locally effective corticosteroids other than budesonide (see Table 9 and Table 17), which, like systemic corticosteroids, should not be used for remission maintenance, according to the S3 guideline. In addition, the proportion of patients who received budesonide as concomitant treatment was balanced between the study arms.

Stool frequency (CDAI-SF) and abdominal pain (CDAI-AP)

Stool frequency by CDAI-SF and abdominal pain by CDAI-AP were the 2 components of the outcome (corticosteroid-free) clinical remission recorded by PRO2. According to the study design, the recording of CDAI-SF and CDAI-AP was prespecified as components of PRO2, but not as independent outcomes. According to the EMA, an instrument for the assessment of clinical response should include clinically important symptoms such as stool frequency and abdominal pain. A clinical response in such an instrument should be defined as response in at least one parameter and no worsening in the other parameters [16]. This was considered adequate in terms of content, as it is a comprehensive representation of symptoms. Irrespective of this, the post hoc analyses of CDAI-SF and CDAI-AP presented in Module 4 A did not concur with the described response criteria prespecified as part of the PRO2. Analyses of the prespecified response criteria were not available, however. Therefore, the responder analyses on stool frequency (CDAI-SF) and abdominal pain (CDAI-AP) were not used for this benefit assessment and are also not presented as components of the outcome corticosteroid-free clinical remission as supplementary information.

Bowel urgency remission (Urgency NRS)

The Urgency NRS is a patient-reported single-item scale that measures the severity of urgency (sudden or immediate need) to have a bowel movement within the last 24 hours using an 11-point scale ranging from 0 (no urgency) to 10 (worst possible urgency) [18]. The question was considered to be face valid.

In Module 4 A of its dossier, the company presented analyses of 2 prespecified responder analyses for the Urgency NRS at Week 52:

- Bowel urgency remission, operationalized as ≤ 2 points

- Decrease (improvement) by ≥ 3 points from baseline

The operationalization as remission (≤ 2 points) concurred with patients being largely symptom-free and was therefore considered valid. This value is also described in the literature as the threshold value for remission [19]. The operationalization as an improvement of ≥ 3 points from baseline was also considered valid: This response criterion was predefined and concurred with at least 15% of the scale range, which, as explained in the *General Methods* of the Institute [1], reflects with sufficient certainty a patient-noticeable change.

Both operationalizations were therefore assessed as valid. However, as the results presented showed that remission was generally achievable in the included patient population and as this represents a more marked improvement, the operationalization as remission was used in the given data situation. This was also due to the fact that the analysis also included patients who had already been in remission at baseline. When operationalized as an improvement of ≥ 3 points, however, only patients for whom an improvement from baseline by the corresponding threshold value was possible were included in the analysis. Regardless of this, there were no significant differences between the study arms for the improvement of ≥ 3 points.

Extraintestinal manifestations

The outcome extraintestinal manifestations was generally assessed as patient relevant. However, the operationalization presented for the outcome was not suitable for the benefit assessment. The operationalization presented in Module 4 A of the dossier included the manifestations arthralgia, arthritis, iritis, uveitis, erythema nodosum, pyoderma gangrenosum and aphthous stomatitis. Deviating from this, the study design specified the outcome to include numerous other manifestations affecting various organs. Furthermore, it remains unclear on what basis the included manifestations were selected by the company. The S3 guideline describes a large number of other extraintestinal manifestations that were neither included in the available nor in the planned operationalization of the outcome, including anaemia, episcleritis/scleritis, hidradenitis suppurativa, psoriasis, liver manifestations, osteopenia, osteoporosis and kidney stones [10].

Irrespective of this, the available analyses on extraintestinal manifestations were also not suitable for the benefit assessment. The outcome was operationalized as the proportion of patients with extraintestinal manifestations at baseline that were resolved by Week 52. Accordingly, only patients who already had extraintestinal manifestations at baseline were included. The analyses therefore did not include patients in whom extraintestinal manifestations only occurred during the study. This was not appropriate. Rather, all patients included in the study should be included in the analysis. The analyses in the clinical study report (CSR) showed that new extraintestinal manifestations occurred during the study, which

were therefore not included in the analyses in Module 4 A. Therefore, the analyses presented for the outcome extraintestinal manifestations were not used for the assessment.

Fistulae

The outcome fistulae was assessed as patient relevant. However, the operationalization as proportion of patients with draining cutaneous fistulae at baseline and closure of all draining cutaneous fistulae at Week 52 presented in Module 4 A of the dossier was not suitable for the benefit assessment. Only patients who already had draining fistulae at baseline were included in the available analyses. The analyses therefore did not include patients in whom draining cutaneous fistulae only occurred during the study. This was not appropriate. Rather, all patients included in the study should be included in the analysis. Therefore, the analyses presented for the outcome fistulae were not used for the assessment.

Fatigue (FACIT-Fatigue)

In Module 4 A of its dossier, the company presented analyses of responder analyses for an improvement at Week 52 by the respective prespecified threshold values ≥ 8 points and ≥ 9 points, which concurred with 15.4% and 17.3% of the scale range of 52 points. In addition, improvements of ≥ 6 or ≥ 7 points were also prespecified response criteria, but these were below 15% of the scale range. As explained in the *General Methods* of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The responder analyses on the FACIT-Fatigue presented by the company thus fulfilled these requirements. In the given situation with numerous prespecified response criteria, the improvement of ≥ 8 points was used for the benefit assessment, as this criterion was closest to 15% of the scale range. It should be noted that in the given data situation, the extent of the effects did not differ between the threshold values of ≥ 8 points and ≥ 9 points.

Activity impairment (WPAI-CD question 6)

The WPAI-CD is a questionnaire developed to measure the impairment of work productivity and of activities outside of work attributable to Crohn's disease [20,21]. In Module 4 A of the dossier, the company presented analyses of the individual question 6 of the WPAI-CD regarding the degree to which Crohn's disease affected daily activities. This question measures the impairment of daily activities in the last 7 days on a scale from 0 to 10 and is face valid.

The available analyses of the WPAI-CD were not suitable for the benefit assessment. Only patients who were in work at baseline were included in the analyses. These were 61% versus 55% of patients in the subpopulation relevant to research question 1, and 58% versus 55% of patients in the subpopulation relevant to research question 2. This means that a relevant

proportion of patients were not included in the analyses. Therefore, the analyses presented for the WPAI-CD were not used.

Health-related quality of life (IBDQ total score and SF-36) as well as bowel symptoms and systemic symptoms (IBDQ symptom scales)

For health-related quality of life, the company presented analyses of the IBDQ total score and of the SF-36, with the IBDQ also including symptom scales for bowel symptoms and systemic symptoms. With regard to the IBDQ total score, the company stated in Module 4 A that it presented responder analyses for the post hoc threshold value of an improvement of ≥ 15%, but did not describe which number of points this threshold value was based on. Since the company correctly stated the scale ranges of the individual domains, it is assumed on the basis of the scale range of the IBDQ total score of 32 to 224 points that the threshold value of 15% was based on a score of 28.8 points. As explained in the *General Methods* of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The responder analyses for the IBDQ submitted by company therefore concurred with the requirements of the methods paper and were used for the benefit assessment.

The symptom scales of the IBDQ include 10 questions on bowel symptoms and 5 questions on systemic symptoms covering patient-relevant aspects of the disease, including incontinence, bloating, haemorrhage, abdominal cramps, nausea, malaise and sleep disorders. These scales therefore represent more symptoms of Crohn's disease than the simple symptom scales CDAI-SF, CDAI-AP and Urgency NRS mentioned above. The symptom scales of the IBDQ thus provide a more comprehensive picture of the symptoms and were therefore used in the given data situation in addition to the total score of the IBDQ, which represents health-related quality of life, to assess the symptoms.

General well-being (CDAI-GWB)

The CDAI-GWB is a patient-reported single-item scale to measure general well-being on a 5-point scale (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible) [22]. To calculate the daily average general well-being, the values were averaged over a period of 7 days. In Module 4 A, the company presented analyses of one post hoc responder analysis for the CDAI-GWB for the improvement by at least 0.6 points (concurring with 15% of the scale range) at Week 52.

According to the study design, the recording of the CDAI-GWB was prespecified as a component of the CDAI, but not as an independent outcome. As the VIVID-1 study involved a prespecified recording of the outcomes health status (by EQ-5D VAS) and health-related quality of life (by IBDQ total score and SF-36, see below), which have overlapping contents

with the construct of general well-being, the post hoc analyses of the CDAI-GWB were not used for the benefit assessment in the given data situation.

Crohn's-related surgeries

Module 4-A did not describe which events were included in the outcome Crohn's-related surgeries. In Module 4 A, the company referred to the case report form (CRF) for information on this aspect. The CRF showed that the given operationalization of the outcome included interventions of notably different grades of severity: On the one hand, it included serious interventions (such as bowel resection), associated with a severe course of disease and potentially severe late complications; on the other hand, it also included less serious interventions (such as surgical closure of a fistula), performed to treat acute symptoms. It is not appropriate to summarize such diverse events. Therefore, the outcome in the operationalization presented was not used for the benefit assessment.

Depression

For the assessment of depression, recorded via the Quick Inventory of Depressive Symptomatology (QIDS-SR16), the company presented analyses on the proportion of patients with an improvement in the QIDS-SR16 total score of at least 4.05 points (corresponding to ≥ 15% of the scale range from 0 to 27) at Week 52. These analyses were not used for the assessment. Depression is a comorbidity of Crohn's disease [10]. Thus, the assessment of depression is not primarily the subject of this assessment. However, assessing mental stress caused by diseases and therapy is a relevant part of an assessment. For the present benefit assessment, a suitable instrument for recording health-related quality of life, IBDQ (see above), which also records aspects of mental health, was available. As described above, the analyses of the IBDQ total score were used for the assessment.

Health status recorded using PGRS and PGIC

In Module 4 A, the company presented analyses of the patient-reported single-item scales Patient Global Rating of Severity (PGRS) and Patient Global Impression of Change (PGIC). However, the study documents contained no information on the wording of the questions. Without knowing the specific wording of the questions, it was not possible to assess the recorded outcome or the validity of the instrument. For this reason, the results for PGRS and PGIC were not used for the benefit assessment. Regardless of this, the results of the responder analyses for PGRS and PGIC presented in Module 4 A, which were generally relevant, showed no statistically significant differences between the study arms.

Outcome category of side effects

The company presented analyses of AEs and SAEs, each including disease-related events. In the given data situation, the overall rates including disease-related events were usable because it was not assumed that the inclusion of disease-related events would mask relevant

effects in side effects (see I Appendix B of the full benefit assessment). However, the high proportions of potentially disease-related events were taken into account in the assessment of the risk of bias (see Section I 4.2.2).

Operationalization of the outcome infections

In the VIVID-1 study, the outcome infections was a prespecified AE of special interest (AESI), operationalized as infections and infestations (SOC according to the Medical Dictionary for Regulatory Activities [MedDRA], AEs). The operationalization of the outcome as infections and infestations (SOC, AEs) was used for the benefit assessment.

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

I 4.2.2 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, direct comparison: mirikizumab vs. ustekinumab

Study		Outcomes													
	Study level	All-cause mortality[a]	Corticosteroid-free clinical remission (PRO2)	Bowel symptoms, systemic symptoms (IBDQ)	Bowel urgency remission (Urgency NRS)	Extraintestinal manifestations	Fistulae	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Activity impairment (WPAI-CD Item 6)	Health-related quality of life (IBDQ, SF-36)	SAEs	Discontinuation due to AEs	Infections[b]	Other specific AEs
VIVID-1	L	H[c]	H[d]	H[d]	H[d]	–[e]	–[e]	H[d]	H[d]	–[e]	H[d]	H[c, f]	L[g]	H[c]	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as infections and infestations (SOC, AEs).
c. Incomplete observations for potentially informative reasons.
d. High proportion of patients with missing values that may not have been adequately imputed.
e. No suitable data available; for the reasoning, see Section I 4.2.1 of this dossier assessment.
f. Disease-related events are also included in the outcome (see Section I 4.2.1).
g. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see running text below).

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; FACIT: Functional Assessment of Chronic Illness Therapy; H: high; IBDQ: Inflammatory Bowel Disease Questionnaire; L: low; NRS: numeric rating scale; PRO2: patient-reported outcome 2 (abdominal pain and stool frequency); RCT: randomized controlled trial; SAE: serious adverse event; SF: stool frequency; SF-36: Short Form 36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

The risk of bias was rated as high for the results for all outcomes except the outcome discontinuation due to AEs.

For the outcomes on morbidity and health-related quality of life, for which suitable data were available, the high risk of bias was due to a high proportion of missing values at Week 52. It is possible that missing values were not adequately imputed. Depending on the outcome, between approximately 13% and 16% of values were missing and imputed in the subpopulation of research question 1. In the subpopulation of research question 2, the proportions of imputed values were between 16% and 20%, depending on the outcome. The majority of the missing values in both subpopulations were due to treatment discontinuations, as according to the study design, no further recordings were made for these outcomes after treatment discontinuation. As prespecified, the company addressed the missing values in its main analysis using non-responder imputation (NRI). This means that for patients with missing values at Week 52, it was assumed that no events in the corresponding outcomes had occurred by Week 52.

The company's assumption that no event had occurred in patients without value by Week 52 could only be partially verified. Data on the response before treatment discontinuation in patients with missing values were not available. However, Module 4 A showed that 13% versus 10% (research question 1) and 27% versus 39% (research question 2) of the patients who discontinued study treatment by Week 52 did so due to lack of efficacy. Another common reason for treatment discontinuation in both subpopulations was patient request (30% versus 43% [research question 1] and 31% versus 26% [research question 2]). However, it was unclear whether patients decided to discontinue treatment due to insufficient efficacy of their treatments. Overall, the analyses based on NRI were subject to uncertainty due to the high proportion of missing values.

In addition, the company presented sensitivity analyses without imputing missing values. These analyses were not used because the NRI analyses had been predefined and, despite their described deficiencies, they were a better method for dealing with missing values than sensitivity analyses without imputation, which did not include patients with missing values.

For the outcomes SAEs and infections, the outcome-specific risk of bias was rated as high. This was due to incomplete observations for potentially informative reasons, as these outcomes were not observed for the entire study duration after treatment discontinuation. Two end-of-study visits were mandated at 4 weeks and at 12 to 16 weeks after treatment discontinuation. However, most treatment discontinuations took place at an early time point (before Week 40), so that the follow-up during the end-of-study visits was not sufficient to cover the entire study period. For the outcome SAEs, another reason for the high outcome-specific risk of bias was that high proportions of potentially disease-related events (especially SAEs of the SOC

gastrointestinal disorders; see Table 24 and Table 27 of the full benefit assessment) were included in the analyses presented (see Section I 4.2.1).

For the outcome discontinuation due to AEs, there was a low risk of bias, but the certainty of the results for this outcome was limited because a high proportion of treatment discontinuations were due to reasons other than AEs. Premature treatment discontinuation for reasons other than AEs was a competing event for the outcome discontinuation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion 'discontinuation' could no longer be applied to them. It was impossible to estimate how many AEs this affected.

Consideration of patients with corticosteroid therapy

According to the VIVID-1 study design, patients who initiated corticosteroid therapy during the study or who received corticosteroid therapy above their individual baseline level were considered non-responders for all efficacy outcomes. However, initiating corticosteroid therapy or increasing the dose of corticosteroids can be part of the treatment strategy in the given therapeutic indication, and also did not necessarily lead to discontinuation of the study medication in the VIVID-1 study. In Module 4 A of its dossier, the company deviated from this prespecification and presented analyses including patients who initiated corticosteroid treatment or increased the corticosteroid dose from baseline, with the values actually recorded and thus without imputation. This approach was adequate.

Analogously, according to the study design, patients with initiation or dose increase of immunosuppressants (6-MP, AZA and/or MTX) were considered non-responders for all efficacy outcomes. However, the proportion of patients who initiated immunosuppressants in the study was low and balanced in both arms (see Table 9 and Table 17). The data in Module 4 A also showed that the proportion of imputed values for reasons other than treatment discontinuation was low and largely balanced in both study arms. Overall, it was therefore not assumed that this had a relevant influence on the results.

Summary assessment of the certainty of conclusions

Based on the VIVID-1 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 4.2.3 Results

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

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) (multipage table)

Study Outcome category Outcome	Mirikizumab		Ustekinumab		Mirikizumab vs. ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
VIVID-1					
Mortality (Week 52)					
All-cause mortality[b]	331	0 (0)	164	1 (0.6)	–
Morbidity (Week 52)					
Corticosteroid-free clinical remission (PRO2)[c]	331	151 (45.6)	164	71 (43.3)	1.04 [0.84; 1.29]; 0.691
Stool frequency (CDAI-SF)				No suitable data[d]	
Abdominal pain (CDAI-AP)				No suitable data[d]	
Clinical remission (PRO-2)[c] (supplementary presentation)	*331*	*182 (55.0)*	*164*	*83 (50.6)*	*1.08 [0.90; 1.29]; 0.411*
Bowel symptoms (IBDQ – improvement[f])	331	225 (68.0)	164	108 (65.9)	1.02 [0.89; 1.16]; 0.774
Systemic symptoms (IBDQ – improvement[g])	331	196 (59.2)	164	98 (59.8)	0.98 [0.84; 1.14]; 0.769
Bowel urgency remission (Urgency NRS)[h]	331	132 (39.9)	164	61 (37.2)	1.06 [0.83; 1.35]; 0.629
Extraintestinal manifestations				No suitable data[d]	
Fistulae				No suitable data[d]	
Fatigue (FACIT-Fatigue – improvement[i])	331	139 (42.0)	164	73 (44.5)	0.93 [0.75; 1.14]; 0.490
Health status (EQ-5D VAS – improvement[j])	331	171 (51.7)	164	89 (54.3)	0.94 [0.79; 1.12]; 0.499
Activity impairment (WPAI-CD Item 6)				No suitable data[d]	
Health-related quality of life (Week 52)					
IBDQ total score (improvement[k])	331	207 (62.5)	164	98 (59.8)	1.03 [0.89; 1.20]; 0.659
Bowel symptoms[f]	331	225 (68.0)	164	108 (65.9)	1.02 [0.89; 1.16]; –
Systemic symptoms[g]	331	196 (59.2)	164	98 (59.8)	0.98 [0.84; 1.14]; –
Emotional functioning[k]	331	184 (55.6)	164	89 (54.3)	1.01 [0.85; 1.20]; –
Social functioning[k]	331	203 (61.3)	164	104 (63.4)	0.96 [0.83; 1.10]; –
SF-36 – improvement[l]					
Physical Component Summary (PCS)	331	152 (45.9)	164	71 (43.3)	1.05 [0.85; 1.29]; 0.656
Mental Component Summary (MCS)	331	96 (29.0)	164	51 (31.1)	0.92 [0.70; 1.22]; 0.581

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) (multipage table)

Study Outcome category Outcome	Mirikizumab N	Mirikizumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Mirikizumab vs. ustekinumab RR [95% CI]; p-value[a]
Side effects (Week 52)					
AEs (supplementary information)	331	245 (74.0)	164	118 (72.0)	–
SAEs	331	22 (6.6)	164	14 (8.5)	0.78 [0.41; 1.48]; 0.465[m]
Discontinuation due to AEs	331	20 (6.0)	164	4 (2.4)	2.48 [0.86; 7.13]; 0.117[m]
Infections[n]	331	131 (39.6)	164	51 (31.1)	1.27 [0.98; 1.66]; 0.075[m]

a. RR stratified by SES-CD total score at baseline (< 12 points vs. ≥ 12 points) and either CDAI-SF ≥ 7 points and/or CDAI-AP ≥ 2.5 points at baseline (yes vs. no/unknown) with associated 95% CI according to the Mantel-Haenszel-Sato method and p-value of the Cochran-Mantel-Haenszel test.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Predefined as the proportion of patients with unweighted daily average SF ≤ 3 and unweighted daily average AP ≤ 1 at Week 52. At the same time, both values at Week 52 were not allowed to be worse than at baseline. For the corticosteroid-free clinical remission, patients were also not allowed to have been treated with corticosteroids between Weeks 40 and 52.
d. See Section I 4.2.1 of this dossier assessment for the reasoning.
e. Defined as CDAI-AP score = 0.
f. A score increase by ≥ 9 points from baseline is considered a clinically relevant improvement (scale range: 10 to 70).
g. A score increase by ≥ 4.5 points from baseline is considered a clinically relevant improvement (scale range: 5 to 35).
h. Defined as Urgency NRS score ≤ 2.
i. A score increase by ≥ 8 points from baseline is considered a clinically relevant improvement (scale range: 0 to 52).
j. A score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
k. A score increase by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 32 to 224 [total score], 12 to 84 [emotional functioning] and 5 to 35 [social functioning]).
l. An increase in PCS by ≥ 9.4 points or in MCS by ≥ 9.6 points from baseline is considered a clinically relevant improvement (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 norm sample [23]).
m. RR without consideration of stratification factors, 95% CI according to Wald and p-value of Fisher's exact test.
n. Operationalized as infections and infestations (SOC, AEs).

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NRS: numeric rating scale; PCS: Physical Component Summary; PRO2: patient-reported outcome 2 (abdominal pain and stool frequency); RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency; SF-36: Short Form-36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

Based on the available information, at most hints, e.g. of an added benefit, could be derived for all outcomes (see Section I 4.2.2 for reasons).

Mortality

All-cause mortality

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

Morbidity

Corticosteroid-free clinical remission (PRO2), bowel symptoms (IBDQ), systemic symptoms (IBDQ), bowel urgency remission (Urgency NRS), fatigue (FACIT-Fatigue) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcomes corticosteroid-free clinical remission (recorded using PRO2), bowel symptoms and systemic symptoms (each recorded using IBDQ), bowel urgency remission (recorded using Urgency NRS), fatigue (recorded using FACIT-Fatigue) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Extraintestinal manifestations, fistulae and activity impairment (WPAI-CD Item 6)

No suitable data were available for the outcomes extraintestinal manifestations, fistulae and activity impairment (recorded using WPAI-CD Item 6) (for reasons, see Section I 4.2.1). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score, SF-36 PCS and SF-36 MCS

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using IBDQ and SF-36). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs and infections (AEs)

There was no statistically significant difference between the treatment groups for any of the outcomes SAEs, discontinuation due to AEs and infections (AEs). There was no hint of greater or lesser harm from mirikizumab in comparison with ustekinumab for any of the outcomes; greater or lesser harm is therefore not proven.

I 4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (< 40 versus ≥ 40 years); the cut-off < 65 versus ≥ 65 years additionally presented by the company was also suitable in principle, but the cut-off < 40 versus ≥ 40 years was used in the given data situation, as the relevant subpopulation comprised only a few patients aged ≥ 65 years (see Section I 4.1.1)
- Sex (male versus female)
- CDAI total score at baseline (< 300 / ≥ 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 1 subgroup.

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

In accordance with the described methods, no relevant effect modification was identified for the outcomes for which suitable data were available.

I 4.3 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 IQWiG *General Methods* [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 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 4.2.3 (see Table 14).

Table 14: Extent of added benefit at outcome level: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) (multipage table)

Outcome category **Outcome**	**Mirikizumab vs. ustekinumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0 vs. 0.6 RR: NC; p = NC	Lesser benefit not proven / added benefit not proven
Morbidity		
Corticosteroid-free clinical remission (PRO2)	45.6 vs. 43.3 RR: 1.04 [0.84; 1.29]; p = 0.691	Lesser benefit not proven / added benefit not proven
Bowel symptoms (IBDQ – improvement)	68.0 vs. 65.9 RR: 1.02 [0.89; 1.16]; p = 0.774	Lesser benefit not proven / added benefit not proven
Systemic symptoms (IBDQ – improvement)	59.2 vs. 59.8 RR: 0.98 [0.84; 1.14]; p = 0.769	Lesser benefit not proven / added benefit not proven
Bowel urgency remission (Urgency NRS)	39.9 vs. 37.2 RR: 1.06 [0.83; 1.35]; p = 0.629	Lesser benefit not proven / added benefit not proven
Extraintestinal manifestations	No suitable data[c]	Lesser benefit not proven / added benefit not proven
Fistulae	No suitable data[c]	Lesser benefit not proven / added benefit not proven
Fatigue (FACIT-Fatigue – improvement)	42.0 vs. 44.5 RR: 0.93 [0.75; 1.14]; p = 0.490	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS – improvement)	51.7 vs. 54.3 RR: 0.94 [0.79; 1.12]; p = 0.499	Lesser benefit not proven / added benefit not proven
Activity impairment (WPAI-CD Item 6)	No suitable data[c]	Lesser benefit not proven / added benefit not proven

Table 14: Extent of added benefit at outcome level: mirikizumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) (multipage table)

Outcome category **Outcome**	**Mirikizumab vs. ustekinumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
IBDQ total score (improvement)	62.5 vs. 59.8 RR: 1.03 [0.89; 1.20]; p = 0.659	Lesser benefit not proven / added benefit not proven
SF-36 Physical Component Summary (PCS – improvement)	45.9 vs. 43.3 RR: 1.05 [0.85; 1.29]; p = 0.656	Lesser benefit not proven / added benefit not proven
SF-36 Mental Component Summary (MCS – improvement)	29.0 vs. 31.1 RR: 0.92 [0.70; 1.22]; p = 0.581	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	6.6 vs. 8.5 RR: 0.78 [0.41; 1.48]; p = 0.465	Greater/lesser harm not proven
Discontinuation due to AEs	6.0 vs. 2.4 RR: 2.48 [0.86; 7.13]; p = 0.117	Greater/lesser harm not proven
Infections (AEs)	39.6 vs. 31.1 RR: 1.27 [0.98; 1.66]; p = 0.075	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 4.2.1 of this dossier assessment for the reasoning.

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; NRS: numeric rating scale; PCS: Physical Component Summary; PRO: patient-reported outcome; RR: relative risk; SAE: serious adverse event; SF: stool frequency; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

I 4.3.2 Overall conclusion on added benefit

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

Table 15: Positive and negative effects from the assessment of mirikizumab in comparison with ustekinumab (research question 1: patients who are not eligible for conventional therapy)

Positive effects	**Negative effects**
–	–
No suitable data are available for the outcomes extraintestinal manifestations, fistulae and activity impairment (WPAI-CD Item 6).	
WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease	

For research question 1 of this benefit assessment, neither positive nor negative effects of mirikizumab compared with ustekinumab were shown in the relevant subpopulation. In summary, there is no hint of an added benefit of mirikizumab versus the ACT for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy. An added benefit is therefore not proven.

The assessment described above concurs with that of the company, which also derived no added benefit for this research question.

I 5 Research question 2: patients who are not eligible for a biologic agent

I 5.1 Study characteristics (specific to research question 2)

For characteristics of the VIVID-1 study that apply to all research questions, see Section I 3.2.

I 5.1.1 Patient characteristics

Table 16 shows the characteristics of the patients in the subpopulation of the included study relevant for research question 2.

Table 16: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Study **Characteristic** **Category**	**Mirikizumab** **N = 300**	**Ustekinumab** **N = 145**
VIVID-1		
Age [years], mean (SD)	36 (13)	36 (12)
Sex [F/M], %	40/60	55/45
Region, n (%)		
Europe	114 (38[a])	50 (34[a])
North America	54 (18)	26 (18)
Other	132 (44[a])	69 (48[a])
Asia	105 (35)	56 (39)
Central or South America	24 (8)	13 (9)
Australia	3 (1)[a]	0 (0)[a]
Time since diagnosis of Crohn's disease [months], mean (SD)	9.3 (9.1)	9.3 (8.5)
Disease location, n (%)		
Colon isolated	120 (40)	59 (41)
Ileum isolated	32 (11)	6 (4)
Ileocolon	148 (49)	80 (55)
SES-CD total score at baseline, mean (SD)	13.8 (6.9)	14.5 (6.8)
CDAI total score at baseline		
Mean (SD)	327.8 (88.9)	326.7 (95.8)
< 220, n (%)	29 (10[a])	12 (8[a])
≥ 220 to < 450, n (%)	244 (83[a])	119 (83[a])
≥ 450, n (%)	20 (7[a])	12 (8[a])
Average stool frequency (CDAI-SF) at baseline, mean (SD)	6.0 (3.4)	6.0 (3.2)
Average abdominal pain (CDAI-AP) at baseline, mean (SD)	2.1 (0.6)	2.0 (0.7)
Average bowel urgency (Urgency NRS) at baseline, mean (SD)	6.7 (2.2)	6.5 (2.2)

Table 16: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Study **Characteristic** **Category**	**Mirikizumab** **N = 300**	**Ustekinumab** **N = 145**
IBDQ total score at baseline, mean (SD)	127.5 (32.7)	126.5 (34.9)
IBDQ bowel symptoms at baseline, mean (SD)	37.8 (9.5)	37.3 (9.9)
IBDQ systemic symptoms at baseline, mean (SD)	17.6 (5.6)	17.7 (5.8)
SF-36 at baseline, mean (SD)		
Physical Component Summary (PCS)	39.2 (8.0)	38.8 (7.9)
Mental Component Summary (MCS)	44.4 (10.7)	45.0 (10.5)
Failure of prior therapy, n (%)		
Prior corticosteroid failure	73 (24)	37 (26)
Prior immunosuppressant failure	130 (43)	53 (37)
Prior TNFα antagonist failure	282 (94)	139 (96)
Prior integrin inhibitor failure	71 (24)	31 (21)
Number of failed biologic therapies, n (%)		
1	192 (64)	97 (67)
2	83 (28)	42 (29)
> 2	25 (8)	6 (4)
Treatment discontinuation in the double-blind phase, n (%)[b]	48 (16)	23 (16)
Study discontinuation, n (%)	ND	ND

a. Institute's calculation.
b. Common reasons for treatment discontinuation in the intervention arm versus the control arm were the following (percentages based on randomized patients): patient decision (5% vs. 4%), lack of efficacy (4% vs. 6%) and AEs (4% vs. 3%). The therapy in the double-blind phase was completed as planned by 252 vs. 122 of the patients.

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; ND: no data; NRS: numeric rating scale; 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

The baseline patient characteristics for the relevant subpopulation in the VIVID-1 study were sufficiently comparable between the 2 treatment arms. The mean age of the patients was 36 years, and only a small proportion (4.3% versus 2.8%) were ≥ 65 years of age. Noticeably, far fewer patients came from the region of Europe in the subpopulation of research question 2 than in research question 1: only about 38% versus 34%, whereas in research question 1 the figures were about 68% versus 74% (see Section I 4.1.1). The company did not discuss these differences between the subpopulations, so the reasons were unclear. In this context, it was also noticeable that in the subpopulation relevant for research question 2, subgroup effects

in the same direction were seen for many outcomes, depending on the characteristic of geographical region. The situation was similar for the characteristic of family origin/ethnicity. This is discussed in more detail in Section I 5.2.4.

The mean of the daily average stool frequency was about 6 and the abdominal pain was approximately 2 (ranging from 0 = no pain to 3 = severe pain). The CDAI total score was in the range of ≥ 220 to < 450 in around 83% of patients. Prior therapy with TNFα antagonists had failed in 94% versus 96% of the patients, and treatment with integrin inhibitors had failed in 24% versus 21%, with failure of only 1 biological therapy regimen in most patients.

The proportion of patients with treatment discontinuation was balanced at around 16% in both study arms; the most common reasons for treatment discontinuation were patient request, lack of efficacy or AEs. No data were available on the proportion of patients with study discontinuation.

I 5.1.2 Concomitant treatments

In its dossier, the company presented the proportion of patients in the relevant subpopulation of the VIVID-1 study who had concomitant treatment with corticosteroids and/or immunosuppressants at baseline or during the study (Table 17).

Table 17: Information on concomitant treatments with corticosteroids and/or immunosuppressants – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent)

Study **Time point** **Drug class**	**Patients with concomitant treatment, n (%)**	
	Mirikizumab **N = 300**	**Ustekinumab** **N = 145**
VIVID-1		
Concomitant treatments at baseline		
Corticosteroids[a]	76 (25.3)[b]	39 (26.9)[b]
Immunosuppressants[c]	66 (22.0)[b]	39 (26.9)[b]
Corticosteroids[a] and immunosuppressants[b]	14 (4.7)	7 (4.8)
Neither corticosteroids[a] nor immunosuppressants[c]	172 (57.3)	74 (51.0)
Concomitant treatments during the study		
Corticosteroids[a]	100 (33.3)[b]	49 (33.8)[b]
Locally effective corticosteroids	21 (7.0)	10 (6.9)
Budesonide	21 (7.0)	10 (6.9)
Beclometasone	1 (0.3)	0 (0)
Immunosuppressants[c]	67 (22.3)[b]	40 (27.6)[b]
Corticosteroids[a] and immunosuppressants[c]	22 (7.3)	12 (8.3)
Neither corticosteroids[a] nor immunosuppressants[c]	155 (51.7)	68 (46.9)

a. Locally administered corticosteroids (e.g. inhaled, intranasal, intra-articular or topical) that were not used for the treatment of Crohn's disease were not included in the calculation.
b. Institute's calculation.
c. For example azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (MTX).

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

The proportion of patients receiving concomitant therapy with corticosteroids and/or immunosuppressants at baseline was balanced between the study arms. The frequency with which concomitant therapies were used during the study was also about equal in both study arms, with around 34% of patients in both arms receiving treatment with systemic corticosteroids during the study.

I 5.1.3 Risk of bias across outcomes (study level)

The risk of bias across outcomes (risk of bias at study level) for the VIVID-1 study, described in Table 10 in Section I 4.1.3, was rated as low.

I 5.1.4 Transferability of the study results to the German health care context

The company's assessment regarding the transferability of the study results to the German health care context is described in Section I 4.1.4.

I 5.2 Results on added benefit

I 5.2.1 Outcomes included

The patient-relevant outcomes that were to be included in the assessment were identical for research questions 1 and 2 and can be found in Section I 4.2.1. The matrix of outcomes presented in this section (Table 11) shows for which outcomes data were available in the included study.

I 5.2.2 Risk of bias

The outcome-specific risk of bias did not differ between research question 1 and research question 2 and can therefore be found in Section I 4.2.2. Based on the VIVID-1 study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented, also for research question 2.

I 5.2.3 Results

Table 18 summarizes the results of the comparison of mirikizumab with ustekinumab in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 18: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Study Outcome category Outcome	Mirikizumab		Ustekinumab		Mirikizumab vs. ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
VIVID-1					
Mortality (Week 52)					
All-cause mortality[b]	300	0 (0)	145	0 (0)	–
Morbidity (Week 52)					
Corticosteroid-free clinical remission (PRO2)[c]	300	118 (39.3)	145	51 (35.2)	1.12 [0.87; 1.46]; 0.367
Stool frequency (CDAI-SF)				No suitable data[d]	
Abdominal pain (CDAI-AP)				No suitable data[d]	
Clinical remission (PRO-2)[c] (supplementary presentation)	*300*	*152 (50.7)*	*145*	*67 (46.2)*	*1.10 [0.90; 1.36]; 0.341*
Bowel symptoms (IBDQ – improvement[f])	300	197 (65.7)	145	90 (62.1)	1.06 [0.91; 1.23]; 0.431
Systemic symptoms (IBDQ – improvement[g])	300	165 (55.0)	145	67 (46.2)	1.20 [0.98; 1.47]; 0.073
Bowel urgency remission (Urgency NRS)[h]	300	119 (39.7)	145	42 (29.0)	1.38 [1.03; 1.85]; 0.024
Extraintestinal manifestations				No suitable data[d]	
Fistulae				No suitable data[d]	
Fatigue (FACIT-Fatigue – improvement[i])	300	109 (36.3)	145	44 (30.3)	1.22 [0.91; 1.62]; 0.170
Health status (EQ-5D VAS – improvement[j])	300	157 (52.3)	145	64 (44.1)	1.20 [0.97; 1.48]; 0.086
Activity impairment (WPAI-CD Item 6)				No suitable data[d]	
Health-related quality of life (Week 52)					
IBDQ total score (improvement[k])	300	167 (55.7)	145	75 (51.7)	1.08 [0.90; 1.31]; 0.390
Bowel symptoms[f]	300	197 (65.7)	145	90 (62.1)	1.06 [0.91; 1.23]; –
Systemic symptoms[g]	300	165 (55.0)	145	67 (46.2)	1.20 [0.98; 1.47]; –
Emotional functioning[k]	300	142 (47.3)	145	66 (45.5)	1.05 [0.85; 1.30]; –
Social functioning[k]	300	161 (53.7)	145	76 (52.4)	1.03 [0.86; 1.24]; –
SF-36 – improvement[l]					
Physical Component Summary (PCS)	300	129 (43.0)	145	60 (41.4)	1.05 [0.83; 1.33]; 0.669
Mental Component Summary (MCS)	300	76 (25.3)	145	36 (24.8)	1.02 [0.72; 1.45]; 0.901

Table 18: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Study Outcome category Outcome	Mirikizumab		Ustekinumab		Mirikizumab vs. ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Side effects (Week 52)					
AEs (supplementary information)	299	250 (83.6)	145	121 (83.4)	–
SAEs	299	43 (14.4)	145	19 (13.1)	1.10 [0.66; 1.81]; 0.772[m]
Discontinuation due to AEs	299	12 (4.0)	145	4 (2.8)	1.45 [0.48; 4.43]; 0.597[m]
Infections[n]	299	130 (43.5)	145	79 (54.5)	0.80 [0.66; 0.97]; 0.033[m]

a. RR stratified by SES-CD total score at baseline (< 12 points vs. ≥ 12 points) and either CDAI-SF ≥ 7 points and/or CDAI-AP ≥ 2.5 points at baseline (yes vs. no/unknown) with associated 95% CI according to the Mantel-Haenszel-Sato method and p-value of the Cochran-Mantel-Haenszel test.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Predefined as the proportion of patients with unweighted daily average SF ≤ 3 and unweighted daily average AP ≤ 1 at Week 52. At the same time, both values at Week 52 were not allowed to be worse than at baseline. For the corticosteroid-free clinical remission, patients were also not allowed to have been treated with corticosteroids between Weeks 40 and 52.
d. See Section I 4.2.1 of this dossier assessment for the reasoning.
e. Defined as CDAI-AP score = 0.
f. A score increase by ≥ 9 points from baseline is considered a clinically relevant improvement (scale range: 10 to 70).
g. A score increase by ≥ 4.5 points from baseline is considered a clinically relevant improvement (scale range: 5 to 35).
h. Defined as Urgency NRS score ≤ 2.
i. A score increase by ≥ 8 points from baseline is considered a clinically relevant improvement (scale range: 0 to 52).
j. A score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
k. A score increase by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 32 to 224 [total score], 12 to 84 [emotional functioning] and 5 to 35 [social functioning]).
l. An increase in PCS by ≥ 9.4 points or in MCS by ≥ 9.6 points from baseline is considered a clinically relevant improvement (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 norm sample [23]).
m. RR without consideration of stratification factors, 95% CI according to Wald and p-value of Fisher's exact test.
n. Operationalized as infections and infestations (SOC, AEs).

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; NRS: numeric rating scale; PCS: Physical Component Summary; PRO2: patient-reported outcome 2 (abdominal pain and stool frequency); RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency; SF-36: Short Form-36 Health Survey; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

Based on the available information, at most hints, e.g. of an added benefit, could be derived for all outcomes (see Section I 4.2.2 for reasons).

Mortality

All-cause mortality

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

Morbidity

Corticosteroid-free clinical remission (PRO2), bowel symptoms (IBDQ), fatigue (FACIT-Fatigue) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcomes corticosteroid-free clinical remission (recorded using PRO2), bowel symptoms (recorded using IBDQ), fatigue (recorded using FACIT-Fatigue) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Extraintestinal manifestations, fistulae and activity impairment (WPAI-CD Item 6)

No suitable data were available for the outcomes extraintestinal manifestations, fistulae and activity impairment (recorded using WPAI-CD Item 6) (for reasons, see Section I 4.2.1). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Bowel urgency remission (Urgency NRS)

There was a statistically significant difference in favour of mirikizumab in comparison with ustekinumab for the outcome bowel urgency remission (recorded using Urgency NRS). For this outcome of the non-serious/non-severe symptoms category, however, the extent of the effect was no more than marginal (see Section I 5.3.1). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab; an added benefit is therefore not proven.

Systemic symptoms (IBDQ)

There was no statistically significant difference between the treatment groups for the outcome systemic symptoms (recorded using the IBDQ). However, there was an effect modification by the characteristic of CDAI total score at baseline (see Section I 5.2.4). For patients with a CDAI total score < 300 at baseline, there was a hint of an added benefit of mirikizumab compared with ustekinumab. For patients with a CDAI total score ≥ 300 at baseline, there was no hint of an added benefit of mirikizumab compared with ustekinumab; an added benefit is therefore not proven for patients with a CDAI total score ≥ 300 at baseline.

Health-related quality of life

IBDQ total score, SF-36 Physical Component Summary (PCS) and SF-36 Mental Component Summary (MCS)

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using IBDQ and SF-36). There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for any of the outcomes; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes of SAEs or discontinuation due to AEs. There was no hint of greater or lesser harm from mirikizumab in comparison with ustekinumab for either of the outcomes; greater or lesser harm is therefore not proven.

Infections (AEs)

There was a statistically significant difference in favour of mirikizumab in comparison with ustekinumab for the outcome infections (AEs). For this outcome of the non-serious/non-severe side effects category, however, the extent of the effect was no more than marginal (see Section I 5.3.1). There was no hint of greater or lesser harm from mirikizumab in comparison with ustekinumab; greater or lesser harm is therefore not proven.

I 5.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (< 40 versus ≥ 40 years); the cut-off < 65 versus ≥ 65 years additionally presented by the company was also suitable in principle, but the cut-off < 40 versus ≥ 40 years was used in the given data situation, as the relevant subpopulation comprised only a few patients aged ≥ 65 years (see Section I 5.1.1)
- Sex (male versus female)
- CDAI total score at baseline (< 300 / ≥ 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 1 subgroup.

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

The results are presented in Table 19.

Table 19: Subgroups (morbidity) – RCT, direct comparison: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent)

Study Outcome Characteristic Subgroup	Mirikizumab N	Mirikizumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Mirikizumab vs. ustekinumab RR [95% CI][a]	Mirikizumab vs. ustekinumab p-value[a]
VIVID-1						
Systemic symptoms (IBDQ – improvement[b])						
CDAI total score at baseline						
< 300	109	57 (52.3)	59	18 (30.5)	1.71 [1.12; 2.62]	0.009
≥ 300	184	106 (57.6)	84	49 (58.3)	0.99 [0.79; 1.23]	1.000
					Interaction:	0.038[c]

a. RR without consideration of stratification factors, 95% CI according to Wald and p-value of Fisher's exact test.
b. A score increase by ≥ 4.5 points from baseline is considered a clinically relevant improvement (scale range: 5 to 35).
c. p-value of the interaction between treatment and subgroup factor from a logistic regression model with the factors treatment, subgroup factor, interaction between treatment and subgroup factor, SES-CD total score at baseline (< 12 points versus ≥ 12 points) and either CDAI-SF ≥ 7 points and/or CDAI-AP ≥ 2.5 points at baseline (yes versus no/unknown).

AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; n: number of patients with (at least one) event; N: number of patients analysed; RCT: randomized controlled trial; RR: relative risk; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency

Morbidity

Systemic symptoms (IBDQ)

For the outcome systemic symptoms (recorded using the IBDQ), there was an effect modification by CDAI total score at baseline. For patients with a CDAI total score < 300 at baseline, there was a statistically significant difference in favour of mirikizumab compared with ustekinumab. There was a hint of an added benefit of mirikizumab in comparison with ustekinumab for this patient group.

For patients with a CDAI total score ≥ 300 at baseline, in contrast, there was no statistically significant difference between the treatment groups. There was no hint of an added benefit of mirikizumab in comparison with ustekinumab for this patient group; an added benefit is therefore not proven.

Results of the subgroup analyses on the characteristic geographical region

There was a marked difference between the research questions in the distribution of patients included in the study within versus outside of Europe (see also Sections I 4.1.1 and I 5.1.1). There was no plausible explanation as to why far fewer patients in Europe were included in research question 2 than in research question 1. Due to this clearly uneven distribution, the results of the subgroup analyses on the characteristic of geographical region were additionally considered as part of this assessment. These showed numerous significant effect modifications that affected almost all key outcomes. Significant advantages were only shown in the region 'other', which included approximately 80% of patients in Asia (see Table 16). Therefore, the results of these subgroup analyses are presented for information in I Appendix C of the full benefit assessment. The situation for the characteristic of family origin/ethnicity was very similar to that of geographical region (the respective analyses are not shown additionally; see Module 4 A, Section 4.3.1.3.2.3.2). It was unclear whether these subgroup effects were due to differences in health care or other, e.g. biological, aspects. In research question 1, there were no relevant effect modifications by the characteristic of geographical region or family origin/ethnicity.

I 5.3 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 IQWiG *General Methods* [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 5.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 5.2.3 (see Table 20).

Determination of the outcome category for symptom outcomes

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

Systemic symptoms (IBDQ)

For systemic symptoms (IBDQ), the mean values at baseline were in the middle of the scale range (see Table 16; scale range: 5 to 35). The company did not provide any information on the threshold value for a classification as severe/serious. Therefore, the outcome bowel

symptoms (IBDQ) was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Bowel urgency remission (Urgency NRS)

For bowel urgency (Urgency NRS), the mean values at baseline were in the middle of the scale range (see Table 16; scale range: 0 to 10). The literature describes that most patients assess values of ≥ 8 points as severe [18]. The company did not provide any information on the threshold value for a classification as severe/serious. Therefore, the outcome bowel urgency remission (Urgency NRS) was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 20: Extent of added benefit at outcome level: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Mirikizumab 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 benefit not proven / added benefit not proven
Morbidity		
Corticosteroid-free clinical remission (PRO2)	39.3 vs. 35.2 RR: 1.12 [0.87; 1.46]; p = 0.367	Lesser benefit not proven / added benefit not proven
Bowel symptoms (IBDQ – improvement)	65.7 vs. 62.1 RR: 1.06 [0.91; 1.23]; p = 0.431	Lesser benefit not proven / added benefit not proven
Systemic symptoms (IBDQ – improvement)		
CDAI total score at baseline		
< 300	52.3 vs. 30.5 RR: 1.71 [1.12; 2.62]; RR: 0.58 [0.38; 0.89][d]; p = 0.009 Probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: minor
≥ 300	57.6 vs. 58.3 RR: 0.99 [0.79; 1.23]; p = 1.000	Lesser benefit not proven / added benefit not proven
Bowel urgency remission (Urgency NRS)	39.7 vs. 29.0 RR: 1.38 [1.03; 1.85]; RR: 0.72 [0.54; 0.97][d]; p = 0.024	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Extraintestinal manifestations	No suitable data[c]	Lesser benefit not proven / added benefit not proven
Fistulae	No suitable data[c]	Lesser benefit not proven / added benefit not proven
Fatigue (FACIT-Fatigue – improvement)	36.3 vs. 30.3 RR: 1.22 [0.91; 1.62]; p = 0.170	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS – improvement)	52.3 vs. 44.1 RR: 1.20 [0.97; 1.48]; p = 0.086	Lesser benefit not proven / added benefit not proven

Table 20: Extent of added benefit at outcome level: mirikizumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Mirikizumab vs. ustekinumab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Activity impairment (WPAI-CD Item 6)	No suitable data[c]	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
IBDQ total score (improvement)	55.7 vs. 51.7 RR: 1.08 [0.90; 1.31]; p = 0.390	Lesser benefit not proven / added benefit not proven
SF-36 Physical Component Summary (PCS – improvement)	43.0 vs. 41.4 RR: 1.05 [0.83; 1.33]; p = 0.669	Lesser benefit not proven / added benefit not proven
SF-36 Mental Component Summary (MCS – improvement)	25.3 vs. 24.8 RR: 1.02 [0.72; 1.45]; p = 0.901	Lesser benefit not proven / added benefit not proven
Side effects		
SAEs	14.4 vs. 13.1 RR: 1.10 [0.66; 1.81]; p = 0.772	Greater/lesser harm not proven
Discontinuation due to AEs	4.0 vs. 2.8 RR: 1.45 [0.48; 4.43]; p = 0.597	Greater/lesser harm not proven
Infections (AEs)	43.5 vs. 54.5 RR: 0.80 [0.66; 0.97]; 0.033	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]

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 4.2.1 of this dossier assessment for the reasoning.
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.

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; MCS: Mental Component Summary; NRS: numeric rating scale; PCS: Physical Component Summary; PRO: patient-reported outcome; RR: relative risk; SAE: serious adverse event; SF: stool frequency; SF-36: Short Form-36 Health Survey; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

I 5.3.2 Overall conclusion on added benefit

Table 21 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 21: Positive and negative effects from the assessment of mirikizumab in comparison with ustekinumab (research question 2: patients who are not eligible for a biologic agent)

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ Systemic symptoms (IBDQ – improvement) ▫ CDAI total score at baseline (< 300): hint of an added benefit – extent: minor	–
No suitable data are available for the outcomes extraintestinal manifestations, fistulae and activity impairment (WPAI-CD Item 6).	
CDAI: Crohn's Disease Activity Index; IBDQ: Inflammatory Bowel Disease Questionnaire; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease	

For research question 2 of this benefit assessment, only one positive effect of mirikizumab compared with ustekinumab was shown in the relevant subpopulation for patients with a CDAI total score < 300 at baseline. This positive effect concerned the outcome systemic symptoms (IBDQ – improvement) and represented a hint of minor added benefit. In the overall assessment of the available results and taking into account the results of the subgroup analyses for the characteristic of geographical region (see Section I 5.2.4), this positive effect in one subgroup was not sufficient to derive an added benefit of mirikizumab in the overall assessment.

In summary, there is no hint of an added benefit of mirikizumab versus the ACT for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor). An added benefit is therefore not proven.

The assessment described above deviates from that of the company, which derived an indication of minor added benefit for this research question.

I 6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of mirikizumab in comparison with the ACT is summarized in Table 22.

Table 22: Mirikizumab – probability and extent of the added benefit

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

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, a change of drug class can be considered as well as a change within the drug class. It is assumed that any possible dose adjustments have already been exhausted.
c. According to the G-BA, continuation of an inadequate therapy does not concur with the specified ACT.
d. The VIVID-1 study did not include any patients who had received risankizumab as prior therapy or who had an inadequate response with, lost response to, or were intolerant to ustekinumab as prior therapy. It remains unclear whether the observed effects can be transferred to the corresponding patients.

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

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

I 7 References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-42.html.