Guselkumab (ulcerative colitis)

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

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned was received within the framework of the present dossier

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	adverse event
AZA	azathioprine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IBDQ	Inflammatory Bowel Disease Questionnaire
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NRI	non-responder imputation
NRS	numerical rating scale
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
RB	rectal bleeding
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SF	stool frequency
SF 7a	Short Form 7a
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TNF	tumour necrosis factor

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug guselkumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 03 June 2025.

Research question

The aim of this report is to assess the added benefit of guselkumab in comparison with the appropriate comparator therapy (ACT) in adult patients with moderately to severely active ulcerative colitis 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 of the benefit assessment of guselkumab

Research question	Therapeutic indication	ACT[a, b, c]
Adults with moderately to severely active ulcerative colitis[d]		
1	Patients who have had an inadequate response to, lost response to, or are intolerant to conventional therapy	Adalimumab or golimumab or infliximab[e] or mirikizumab or ozanimod or ustekinumab or vedolizumab
2	Patients 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 filgotinib or golimumab or infliximab or mirikizumab or ozanimod or tofacitinib or upadacitinib or ustekinumab or vedolizumab

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Switching within or between drug classes is permitted. Any potential dose adjustment options are assumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.
c. Guselkumab is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
e. If infliximab is used, it should be combined with a thiopurine, if necessary.

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

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

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

Study pool and study design

The VEGA study comparing guselkumab with golimumab was used for the benefit assessment. The VEGA study is a completed, double-blind RCT with a total of three arms. The study

compared combination therapy with guselkumab + golimumab with the respective monotherapies guselkumab and golimumab. Only the comparison of monotherapy with guselkumab versus monotherapy golimumab is relevant for this benefit assessment. The study included adult patients with moderately to severely active ulcerative colitis who were naive to TNF-α inhibitors and had an inadequate response with, lost response to, or were intolerant to conventional therapy with oral or intravenous corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]). The confirmed diagnosis of ulcerative colitis must have been established at least 3 months before enrolment. The severity of the disease was determined using the Mayo score, which had to be at least 6 points in the total score with at least 2 points in the endoscopy subscore at baseline.

The VEGA study included a total of 143 patients in the relevant treatment arms who were randomly assigned in a 1:1 ratio to the intervention arm (N = 71) or the control arm (N = 72). Randomization was stratified according to treatment with corticosteroids at baseline (yes vs. no). In order to maintain blinding throughout the entire study duration, a placebo was additionally used in both arms.

The treatment duration was 38 weeks or until the initiation of a non-permitted concomitant medication, colectomy, development of an opportunistic infection, occurrence of further specific adverse events (AEs), treatment discontinuation following a decision by the investigator or at the patient's request.

Primary outcome of the VEGA study was clinical response at Week 12, measured as an improvement in the Mayo score by ≥ 30% and ≥ 3 points compared to baseline, accompanied by a reduction in the subscore for rectal bleeding (RB) by ≥ 1 point or a subscore for RB of 0 or 1 point. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Data cut-offs

Three data cut-offs were performed for the VEGA study:

- First data cut-off of April 2020: prespecified interim analysis at Week 12
- Second data cut- off of 01 December 2020: prespecified primary analysis of the outcomes of the morbidity and health-related quality of life categories at Week 38
- Third data cut-off of 15 November 2021: prespecified final analysis of the outcomes in the side effects category at Week 50

Data on morbidity and patient-reported outcomes were only recorded up to Week 38. In contrast, the final follow-up for safety and tolerability was conducted up to 16 weeks after the last dose of the study medication, which corresponds to a total observation period of 50

weeks. The second data cut-off was used for morbidity and health-related quality of life, and the third data cut-off was used for the side effects category.

Risk of bias

The risk of bias across outcomes was rated high, as the statistical analysis plan (SAP) may have been created with knowledge of the data. This led to a high risk of bias for the results of all outcomes.

Since no suitable data are available for the outcome symptomatic remission, the risk of bias for this outcome is not assessed.

In addition to the high risk of bias across outcomes and the outcome-specific risk of bias, the following uncertainty exists for the results of the VEGA study, which has an impact on the certainty of conclusions:

- administration of study medication in the intervention and control arms not fully compliant with the Summary of Product Characteristics (SmPC)

Overall, due to the mentioned uncertainties in the VEGA study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

Results

Mortality

Overall survival

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 guselkumab in comparison with golimumab; an added benefit is therefore not proven.

Morbidity

Symptomatic remission

No suitable data are available for the outcome symptomatic remission, as the operationalization of the outcome presented does not cover relevant aspects of an added benefit of guselkumab in comparison with golimumab; an added benefit is therefore not proven.

Bowel symptoms (Inflammatory Bowel Disease Questionnaire [IBDQ]), systemic symptoms (IBDQ), fatigue (Patient-Reported Outcome Measurement Information System [PROMIS] Fatigue Short Form 7a [SF7a])

For the outcomes bowel symptoms (recorded using the IBDQ), systemic symptoms (recorded using the IBDQ) and fatigue (recorded using the PROMIS Fatigue SF7a), there was no

statistically significant difference between the treatment groups. There was no hint of an added benefit of guselkumab over golimumab; an added benefit is therefore not proven.

Patient Global Impression of Change (PGIC)

A statistically significant difference between treatment groups in favour of guselkumab was shown for the outcome PGIC. The difference, however, is no more than marginal for this outcome of the category non-serious/non-severe symptoms/late complications. There was no hint of an added benefit of guselkumab in comparison with golimumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

No statistically significant difference between treatment groups was found for the outcome health-related quality of life (recorded using the IBDQ total score). There was no hint of an added benefit of guselkumab in comparison with golimumab; an added benefit is therefore not proven.

PROMIS-29

No data were available for the Physical Component Summary (PCS) and the Mental Component Summary (MCS) of the PROMIS-29. There was no hint of an added benefit of guselkumab over golimumab; an added benefit is therefore not proven.

Physical functioning, anxiety, depression, exhaustion, pain interference and pain intensity

No statistically significant differences between the treatment groups were found for the domains physical functioning, anxiety, depression, exhaustion, pain interference and pain intensity. There was no hint of an added benefit of guselkumab over golimumab; an added benefit is therefore not proven.

Sleep interference and participation in social roles and activities

For the domains sleep interference and participation in social roles and activities, there is a statistically significant difference in favour of guselkumab in comparison with golimumab. In each case, this results in a hint of an added benefit of guselkumab in comparison with golimumab.

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 serious AEs (SAEs), discontinuation due to AEs and infections (AEs). Consequently, there is no hint of greater or lesser harm from guselkumab in comparison with golimumab for either of them; greater or lesser harm is therefore not proven.

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

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

For research question 1 of this benefit assessment, guselkumab shows positive effects compared to golimumab in the domains sleep interference and participation in social roles and activities of the PROMIS-29. In this dossier, the company has not submitted the PCS and the MCS of the PROMIS-29. The observed positive effects of guselkumab in the two individual domains of the PROMIS-29 only reflect partial aspects of health-related quality of life. Overall, however, these effects are not sufficient to justify the derivation of a minor added benefit for the comprehensive concept of health-related quality of life in the present data situation.

In summary, there is no hint of an added benefit of guselkumab versus the ACT for patients 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

Results

The review of the information retrieval did not identify any relevant study for research question 2. In Module 4C, the company describes the pivotal studies QUASAR Induction Study 1, QUASAR Induction Study 2 and QUASAR Maintenance Study as supportive information to assess the efficacy and tolerability of guselkumab. This study compared guselkumab with placebo. A comparison versus the ACT is therefore not available. The company did not claim an added benefit.

Results on added benefit

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

[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].

Probability and extent of added benefit – summary

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

Table 3: Guselkumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b, c]	Probability and extent of added benefit
Adults with moderately to severely active ulcerative colitis[d]			
1	Patients who have had an inadequate response to, lost response to, or are intolerant to conventional therapy	Adalimumab or golimumab or infliximab or mirikizumab or ozanimod or ustekinumab or vedolizumab	Added benefit not proven
2	Patients 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 filgotinib or golimumab or infliximab or mirikizumab or ozanimod or tofacitinib or upadacitinib or ustekinumab or vedolizumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Switching within or between drug classes is permitted. Any potential dose adjustment options are assumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.
c. Guselkumab is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
e. If infliximab is used, it should be combined with a thiopurine, if necessary.

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 guselkumab in comparison with the ACT in adult patients with moderately to severely active ulcerative colitis 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 of the benefit assessment of guselkumab

Research question	Therapeutic indication	ACT[a, b, c]
Adults with moderately to severely active ulcerative colitis[d]		
1	Patients who have had an inadequate response to, lost response to, or are intolerant to conventional therapy	Adalimumab or golimumab or infliximab or mirikizumab or ozanimod or ustekinumab or vedolizumab
2	Patients 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 filgotinib or golimumab or infliximab or mirikizumab or ozanimod or tofacitinib or upadacitinib or ustekinumab or vedolizumab

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Switching within or between drug classes is permitted. Any potential dose adjustment options are assumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.
c. Guselkumab is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
e. If infliximab is used, it should be combined with a thiopurine, if necessary.

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

To determine the ACT, the company's dossier refers to a consultation meeting held on 28 May 2020 [3] and the decision of the last benefit assessment procedure for the same therapeutic indication dated 20 February 2025 [4]. For research question 1, the company considers adalimumab, golimumab, infliximab, ozanimod, ustekinumab or vedolizumab, and for research question 2, it considers adalimumab, filgotinib, golimumab, infliximab, ozanimod, tofacitinib, ustekinumab or vedolizumab to be comprised in the ACT. The G-BA updated the ACT on 6 May 2025 and additionally specified mirikizumab for research question 1 and mirikizumab and upadacitinib for research question 2 as part of the ACT. In doing so, the company departed from the updated specification by the G-BA. This has no consequences for this benefit assessment. A check of the completeness of the study pool as part of this benefit assessment did not identify any study comparing guselkumab with mirikizumab or upadacitinib (see Sections I 3.1 and I 4.1).

The assessment of the added benefit was conducted in comparison with the G-BA's updated ACT presented in Table 4.

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 the added benefit. This concurred with the company's inclusion criteria.

I 3 Research question 1: patients who are not eligible for conventional therapy

I 3.1 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 guselkumab (status: 16 April 2025)
- Bibliographical literature search on guselkumab (last search on 16 April 2025)
- Search in trial registries/trial results databases for studies on guselkumab (last search on 16 April 2025)
- Search on the G-BA website for etrasimod (last search on 16 April 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on guselkumab (last search on 12 June 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: guselkumab vs. the 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])
CNTO1959UCO2002 (VEGA[c])	Yes[d]	Yes	No	Yes [5,6]	Yes [7,8]	Yes [9]

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.
c. In the tables below, the study will be referred to using this acronym.
d. In the context of the marketing authorization, this study was only used to support the safety evaluation.

ACT: appropriate comparator therapy; RCT: randomized controlled trial

The VEGA study comparing guselkumab with golimumab was used for the benefit assessment. The study pool was consistent with that selected by the company.

I 3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
VEGA	RCT, double-blind, parallel	Adult patients with moderately to severely active ulcerative colitis[b] ▪ untreated with TNF-α inhibitors ▪ with intolerance, inadequate response or loss of response to conventional therapy with oral or intravenous corticosteroids[c] or immunomodulators (6-MP or AZA)[d]	Guselkumab (N = 71) vs. golimumab (N = 72) guselkumab + golimumab (N = 71)[e]	Screening: ≤ 8 weeks treatment: 38 weeks[f] observation: 50 weeks[f]	54 study centres in Argentina, Australia, Brazil, Germany, Mexico, Poland, Russia, Ukraine, United States 11/2018 – 11/2021 data cut-offs: 04/2020[g] 1 December 2020[h] 15 November 2021[i]	Primary: clinical response at Week 12[j] 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. Based on a Mayo score of ≥ 6 points with an endoscopy subscore of ≥ 2 points at baseline. The diagnosis had to be clinically confirmed ≥ 3 months prior to enrolment.
c. Criteria for the failure of corticosteroids:
- Corticosteroid-refractory disease, defined as signs of inadequate response, recurrence of disease or relapse despite administration of at least 0.75 mg/kg/day or ≥ 40 mg/day of prednisone (or corticosteroid equivalent, orally or intravenously) for 2 weeks or ≥ 9 mg/day of budesonide orally or ≥ 5 mg/day of beclomethasone dipropionate orally for at least 4 weeks.
- Intolerance to corticosteroids, defined as the development of a clinically significant AE (e.g. osteonecrosis or osteoporosis, psychosis, uncontrolled diabetes) that has not responded to a dose reduction and which, in the investigator's opinion, precludes the use of corticosteroids for the treatment of ulcerative colitis, or defined as a medical condition that precludes the use of corticosteroids for the treatment of ulcerative colitis.
- Corticosteroid dependence, defined as failure to reduce or discontinue corticosteroids within 3 months of starting therapy (e.g. due to a flare of the disease) or as relapse within 3 months of discontinuing corticosteroids.

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
d. Criteria for the failure of immunomodulators: ▫ Refractory disease against immunomodulators, defined as signs of inadequate response, recurrence of the disease or relapse despite administration of 1 mg/kg/day 6-MP or 2 mg/kg/day AZA for ≥ 3 months or a lower dosage of 6-MP or AZA (if required by national or local guidelines), or the highest tolerated dose (due to leukopenia, elevated liver enzymes, or nausea), or although the dosage of 6-MP or AZA was confirmed to be therapeutically effective (thioguanine-nucleotid level in the whole blood of > 200 pmol/8x10^8 erythrocytes. ▫ Intolerance to immunomodulators, defined as the development of a clinically significant AE (e.g. pancreatitis, arthritis accompanied by high pyrexia and/or skin rash, leukopenia or persistently increased hepatic enzymes) within the last 5 years, which has not responded to a dose reduction and which, in the investigator's opinion, precludes the use of 6-MP or AZA for the treatment of ulcerative colitis, or defined as a medical condition that precludes the use of 6-MP or AZA for the treatment of ulcerative colitis. e. This arm involves a 12-week combination therapy with guselkumab + golimumab followed by a 26-week monotherapy with guselkumab. The arm is not relevant for the benefit assessment and is therefore not presented in the following tables. f. The last dose of the study medication was administered at Week 34. Further investigations (e.g. PRO recordings) were conducted at Week 38. A final follow-up was conducted for all patients 16 weeks after the last administration of the study medication. For patients who did not discontinue treatment prematurely, this corresponded to a total observation period of 50 weeks. g. Interim analysis after 12 weeks of treatment; the company did not provide any information on the exact date of the data cut-off. h. The primary analysis was conducted after 38 weeks of treatment. i. The final analysis was conducted after 50 weeks of observation. j. Measured by an improvement in the Mayo score by ≥ 30% and ≥ 3 points compared to baseline with a reduction in the RB score by ≥ 1 or an RB score of 0 or 1. 6-MP: 6-mercaptopurine; AE: adverse event; AZA: azathioprine; UC: ulcerative colitis; N: number of randomized patients; PRO: patient-reported outcomes; RCT: randomized controlled trial; TNF: tumour necrosis factor						

Table 7: Characteristics of the interventions – RCT, direct comparison: guselkumab vs. golimumab (multipage table)

Study	Intervention	Comparison
VEGA	Guselkumab ▪ 200 mg IV at Weeks 0, 4 and 8 ▪ 100 mg SC at Weeks 16, 24 and 32[a]	Golimumab ▪ 200 mg SC at Week 0 ▪ 100 mg SC every 4 weeks from Week 2 to Week 34[b]
	Dose adjustment: not allowed	
	Required pretreatment ▪ conventional therapies: corticosteroids and/or immunomodulators (6-MP or AZA) **disallowed prior and concomitant treatment** ▪ TNFα inhibitors ▪ IL-12 or IL-23 inhibitors <u>after study inclusion:</u> ▫ natalizumab[c] ▫ drugs that degrade B-cells or T cells (e.g. rituximab, alemtuzumab)[d] ▫ thalidomide or related drugs ▫ other immunomodulatory biologics and investigational IBD drugs <u>from 2 weeks before first administration of the study medication:</u> ▫ immunomodulators (6-MP, AZA or MTX) ▫ rectal and parenteral corticosteroids[e] ▫ rectal 5-ASA preparations[e] ▫ complete parenteral nutrition or enteral nutrition for the treatment of UC[e] ▫ antibiotics for the treatment of UC (e.g. ciprofloxacin, metronidazole or rifaximin)[e] ▫ apheresis (e.g. adacolumn or cellsorba) <u>from 4 weeks before first administration of the study medication</u> ▫ JAK inhibitors[f] ▫ cyclosporin, mycophenolate mofetil, tacrolimus or sirolimus ▫ 6-thioguanine ▫ investigational preparations[f] <u>from 18 weeks before first administration of the study medication</u> ▫ Vedolizumab **allowed concomitant treatment[g]** ▪ oral 5-ASA preparations[h] ▪ oral corticosteroids[h, i, j]	

a. To maintain blinding, a subcutaneous placebo was additionally administered at Weeks 0 and 2 and thereafter every 4 weeks up to Week 34.
b. To maintain blinding, an intravenous placebo was additionally administered at Weeks 0, 4 and 8 and a subcutaneous placebo was administered at Weeks 16, 24 and 38.
c. According to the company up to 12 months after the start of treatment. This statement from the SP (exclusion criteria at screening for the study) is not plausible.
d. According to the company, up to 12 months after start of the therapy, or if a depletion of B- or T-cells can still be confirmed ≥ 12 months after completion of the therapy with lymphocyte-depleting drugs. This statement from the SP (exclusion criteria at screening for the study) is not plausible.

Table 7: Characteristics of the interventions – RCT, direct comparison: guselkumab vs. golimumab (multipage table)

Study	Intervention	Comparison
e. If therapy was initiated or an existing dosage was changed due to medical necessity, patients continued to attend all scheduled study visits. This was not considered a deviation from the study protocol, but could possibly be assessed as treatment failure. f. Or ≤ 5 half-lives, whichever is longer. g. An initiation of these drugs is not permitted during the study. h. Stable dose for ≥ 2 weeks before the first administration of the study medication; if this concomitant treatment was discontinued, this had to be done ≥ 2 weeks before the first administration of the study medication. i. Daily dose equivalent to ≤ 20 mg prednisone (except for budesonide or beclomethasone dipropionate). j. From Week 6 onwards, all patients who were taking oral corticosteroids at the start of the study had to start dose reduction up to the discontinuation of the corticosteroids, unless this was not possible for medical reasons. 5-ASA: 5-aminosalicylic acid; 6-MP: 6-mercaptopurine; AZA: azathioprine; UC: ulcerative colitis; IV: intravenous; IBD: inflammatory bowel disease; IL: interleukin; JAK: Janus kinase; MTX: methotrexate; RCT: randomized controlled trial; SC: subcutaneous; SP: study protocol; TNF: tumour necrosis factor		

The VEGA study is a completed, double-blind RCT with a total of three arms. The study compared combination therapy with guselkumab + golimumab with the respective monotherapies guselkumab and golimumab. Only the comparison of monotherapy with guselkumab versus monotherapy golimumab is relevant for this benefit assessment. The study included adult patients with moderately to severely active ulcerative colitis who were naive to TNF-α inhibitors and had an inadequate response with, lost response to, or were intolerant to conventional therapy with oral or intravenous corticosteroids or immunomodulators (6-MP or AZA). The confirmed diagnosis of ulcerative colitis must have been established at least 3 months before enrolment. The severity of the disease was determined using the Mayo score, which had to be at least 6 points in the total score with at least 2 points in the endoscopy subscore at baseline. Previous therapy with immunomodulators, rectal or parenteral corticosteroids, or rectal 5-aminosalicylic acid (5-ASA) had to be discontinued prior to study enrolment. However, therapy with oral 5-ASA or oral corticosteroids at a stable dosage was permitted if this medication had been received at the start of the study. In the case of treatment with oral corticosteroids, a dose reduction had to be started 6 weeks after study inclusion, unless this was not possible for medical reasons.

The VEGA study included a total of 143 patients in the relevant treatment arms who were randomly assigned in a 1:1 ratio to the intervention arm (N = 71) or the control arm (N = 72). Randomization was stratified according to treatment with corticosteroids at baseline (yes vs. no). In order to maintain blinding throughout the entire study duration, a placebo was additionally used in both arms.

The treatment duration was 38 weeks or until the initiation of a non-permitted concomitant medication, colectomy, development of an opportunistic infection, occurrence of further specific AEs, treatment discontinuation following a decision by the investigator or at the patient's request. The final follow-up for safety and tolerability, as well as ulcerative colitis-related hospitalization, emergency room admissions and surgeries, was conducted up to 16 weeks after the last administration of the study medication, corresponding to a total observation period of 50 weeks. Information on whether patients received subsequent treatment or were undergoing treatment for ulcerative colitis during the 16-week follow-up period was not reported for the VEGA study.

Primary outcome of the VEGA study was clinical response at Week 12, measured as an improvement in the Mayo score by ≥ 30% and ≥ 3 points compared to baseline, accompanied by a reduction in the subscore for RB by ≥ 1 point or a subscore for RB of 0 or 1 point. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Data cut-offs

Three data cut-offs were performed for the VEGA study:

- first data cut-off of April 2020: prespecified interim analysis at Week 12
- second data cut- off of 01 December 2020: prespecified primary analysis of the outcomes of the morbidity and health-related quality of life categories at Week 38
- third data cut-off of 15 November 2021: prespecified final analysis of the outcomes in the side effects category at Week 50

Data on morbidity and patient-reported outcomes were only recorded up to Week 38. In contrast, the final follow-up for safety and tolerability was conducted up to 16 weeks after the last dose of the study medication, which corresponds to a total observation period of 50 weeks. The second data cut-off was used for morbidity and health-related quality of life, and the third data cut-off was used for the side effects category.

Limitations of the VEGA study

Preparation of the SAP possibly with knowledge of the data

As described in the previous section, three data cut-offs were performed in the VEGA study, with the database locked at Week 12, Week 38 and Week 50. For this benefit assessment, the data cut-off at Week 38 (2nd data cut-off) is relevant for the results in the outcome categories morbidity and health-related quality of life, and the data cut-off at Week 50 (third data cut-off) is relevant for the results in the outcome categories mortality and side effects. In its dossier, the company submitted a total of four versions of the SAP. The oldest SAP dated 6 September 2019 relates exclusively to the Data Monitoring Committee of the VEGA study.

Two further SAPs (including one amendment) dated 20 April 2020 and 27 April 2020 relate exclusively to the interim analysis at Week 12 of the VEGA study and include a reduced selection of outcomes and operationalizations compared to the SAP for the primary and final analysis. The SAP for the analysis of the VEGA study at Weeks 38 and 50 was created on 24 February 2021, almost three months after the date of the second data cut-off (1 December 2020). It can therefore not be ruled out that the SAP was drawn up with knowledge of the data from the VEGA study and was thus results-driven. This uncertainty is taken into account when assessing the risk of bias.

Intervention and comparator therapy not administered in full compliance with the SmPC

In the VEGA study, both the intervention with guselkumab and the comparator therapy with golimumab were not administered in full compliance with the SmPC.

According to the SmPC, guselkumab should be administered to patients with ulcerative colitis at an induction dose of 200 mg as an intravenous injection in Weeks 0, 4 and 8, followed by a maintenance dose of 100 mg as a subcutaneous injection every 8 weeks from Week 16 onwards. For patients who do not experience sufficient therapeutic benefit after the induction phase, a maintenance dose of 200 mg guselkumab should be administered as a subcutaneous injection every 4 weeks from Week 12 onwards [10]. Such a maintenance dose for patients without sufficient therapeutic benefit was not provided for in the VEGA study. According to the company's information for the primary outcome, a total of 18 (25%) patients showed no clinical response at Week 12. These patients may have benefited from a higher maintenance dose.

According to the SmPC, golimumab should be administered as a subcutaneous injection to patients with ulcerative colitis in a weight-dependent dosage. For patients weighing < 80 kg, an initial dose of 200 mg should be administered at Week 0, and 100 mg at Week 2, followed by a maintenance dose of 50 mg every 4 weeks from Week 6 onwards for patients with a clinical response to therapy, or 100 mg every 4 weeks for patients with an inadequate clinical response to therapy. For patients weighing ≥ 80 kg, an initial dose of 200 mg should be administered at Week 0, and 100 mg at Week 2, followed by a maintenance dose of 100 mg every 4 weeks [11]. The VEGA study did not include weight-based dosing or dosing based on clinical response for golimumab. All patients received an initial dose of 200 mg at Week 0, 100 mg at Week 2 and a maintenance dose of 100 mg every 4 weeks, regardless of weight and clinical response. The proportion of patients weighing < 80 kg or ≥ 80 kg in the study cannot be learned from the information provided by the company. The median weight of patients in the control arm was 71.7 kg. Thus, in the VEGA study, the dosage deviated from the weight-based recommendation in the SmPC in at least 50% of patients. An insufficient response according to the primary outcome of the VEGA study, which could justify the maintenance dose of 100 mg every 4 weeks used in the study in patients weighing < 80 kg, was observed in

39% of patients in the control arm at Week 12. However, it remains unclear how the proportions of patients with an inadequate response at Week 12 (primary outcome of the VEGA study) and at Week 6 (relevant time point for assessing clinical response according to the SmPC for golimumab) are distributed across the patient populations weighing < 80 kg and ≥ 80 kg, respectively.

Overall, it is unclear to what extent the deviations from the SmPC in the intervention and the control arm have an impact on 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 3.2.2).

Patient characteristics

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: guselkumab versus golimumab (multipage table)

Study characteristic category	Guselkumab N = 71	Golimumab N = 72
VEGA		
Age [years], mean (SD)	39 (14)	38 (10)
Sex [F/M], %	44/56	42/58
Region, n (%)		
Eastern Europe	58 (82)	61 (85)
Latin America	6 (8)	4 (6)
Rest of the world[a]	7 (10)	7 (10)
Body weight (kg)		
Mean (SD)	69.6 (16.7)	73.9 (17.1)
Median [Q1; Q3]	68 [55.5; 79]	71.7 [60.6; 87.3]
Tobacco use, n (%)		
Non-smoker	56 (79)	62 (86)
Former smoker	11 (15)	7 (10)
Smoker	4 (6)	3 (4)
Duration of UC [years], median [Q1; Q3]	3.3 [2.1; 6.7]	4.0 [1.0; 6.3]
Mayo score[b], median [Q1; Q3]	9 [8; 10]	9 [8; 10]
Endoscopic subscore[c], n (%)		
Moderate (subscore = 2)	24 (34)	35 (49)
Severe (subscore = 3)	47 (66)	37 (51)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: guselkumab versus golimumab (multipage table)

Study characteristic category	**Guselkumab N = 71**	**Golimumab N = 72**
Stool frequency subscore[d], n (%)		
Subscore = 1	7 (10)	12 (17)
Subscore = 2	31 (44)	27 (37)
Subscore = 3	33 (46)	33 (46)
Rectal bleeding, n (%)		
Subscore = 1	23 (32)	22 (31)
Subscore = 2	41 (58)	45 (63)
Subscore = 3	5 (7)	3 (4)
No data	2 (3)	2 (3)
Global assessment by the physician[f], n (%)		
Subscore = 1	ND	ND
Subscore = 2	ND	ND
Subscore = 3	ND	ND
Severity of the UC, n (%)		
Moderate (6 ≤ Mayo score ≤ 10)	64 (90)	63 (88)
Serious (Mayo score > 10)	7 (10)	9 (12)
Study participants with prior treatment with biologics or JAK inhibitors, n (%)	4 (6)	1 (1)
Study participants with ≥ 1 concomitant treatment for UC at baseline, n (%)	66 (93)	66 (92)
Corticosteroid use at baseline, n (%)		
Yes	28 (39)	31 (43)
No	43 (61)	41 (57)
Study participants who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, n (%)	71 (100)	72 (100)
Corticosteroids[g], n (%)	64 (90)	65 (90)
Inadequate response	31 (44)	32 (44)
Dependence	39 (55)	32 (44)
Intolerance	10 (14)	10 (14)
Immunomodulators (6-MP/AZA)[g], n (%)	24 (34)	19 (26)
Inadequate response	16 (23)	15 (21)
Intolerance	9 (13)	5 (7)
Treatment discontinuation[h], n (%)[i]	6 (8)	13 (18)
Study discontinuation[j], n (%)[k]	11 (15)	13 (18)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: guselkumab versus golimumab (multipage table)

Study characteristic category	Guselkumab N = 71	Golimumab N = 72
a. Australia, Germany, USA. b. The total score ranges from 0 to 12 points and comprises the four subscores stool frequency, rectal bleeding, endoscopic findings and global assessment by the physician. c. 0 = normal or inactive disease; 1 = mild disease (erythema, reduced vascular pattern, mild friability); 2 = moderate disease (pronounced erythema, absent vascular pattern, friability, erosions); 3 = severe disease (spontaneous bleeding, ulcerations). d. 0 = normal number of stools (compared to the patient-reported number of daily stools before the disease or during remission of the disease); 1 = 1-2 stools more than normal; 2 = 3-4 stools more than normal; 3 = ≥ 5 stools more than normal. e. 0 = no blood in stool; 1 = traces of blood in < 50% of stools; 2 = mostly obvious blood in stools; 3 = stools consisting exclusively of blood. f. 0 = normal; 1 = mild disease; 2 = moderate disease; 3 = severe disease. g. Multiple answers possible. h. Up to Week 34 (last administration of study medication). i. Common reasons for treatment discontinuation in the intervention arm versus the control arm were the following (percentages based on randomized patients): patient's request (1% vs. 8%), lack of improvement of the disease (0% vs. 6%), lack of efficacy (3% versus 3%). 92% vs. 82% of the patients completed treatment as planned. j. Up to Week 50. k. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): patient's request (1% vs. 11%), conditions related to COVID-19 (9% vs. 3%), other (10% vs. 4%). The data additionally include patients who died during the course of the study (intervention arm: 1% vs. control arm: 0%). 6-MP: 6-mercaptopurine; AZA: azathioprine; JAK: Janus kinase; f: female; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; UC: ulcerative colitis		

Both treatment arms are largely balanced in terms of the demographic and clinical characteristics of the patients in the VEGA study. The mean patient age was 39 and 38 years; most of them were male (56% versus 58%) and the majority came from Eastern Europe (82% versus 85%). In both treatment arms, patients had a median Mayo score of 9 points. The median duration of ulcerative colitis was 3.3 months for patients in the intervention arm and 4.0 months for patients in the control arm. A total of 39% and 43% of patients received corticosteroid therapy at baseline. Overall, 90% of patients in both arms showed an inadequate response, intolerance or dependence when treated with corticosteroids. In addition, 34% and 26% of patients showed an inadequate response or intolerance to immunomodulators (6-MP or AZA), respectively. A small proportion of 5 patients (4 vs. 1) had been treated with a biologic agent or a Janus kinase inhibitor in a previous therapy. However, due to the small proportion, this has no impact on the assessment of research question 1.

The proportion of patients who discontinued treatment was lower in the intervention arm than in the control arm (8% vs. 18%). The most frequent reasons for treatment discontinuation were patient's request (1% vs. 11%) and AEs (1% vs. 6%). The number of dropouts differs only slightly between the treatment arms (15% vs. 18%).

Concomitant treatments

Table 9 shows concomitant treatment with aminosalicylates and/or corticosteroids at the start of the study and during the course of the study.

Table 9: Information on concomitant therapies with aminosalicylates and/or corticosteroids – RCT, direct comparison: guselkumab vs. golimumab

Study time point drug class	Patients with concomitant treatment, n (%)	
	guselkumab N = 71	golimumab N = 72
VEGA		
UC concomitant therapies at baseline		
Aminosalicylates	63 (88.7)	62 (86.1)
Mesalamine	59 (83.1)	59 (81.9)
Mesalazine	0 (0)	0 (0)
Sulfasalazine	4 (5.6)	3 (4.2)
Corticosteroids[a]	28 (39.4)	31 (43.1)
Budesonide	4 (5.6)	6 (8.3)
Dexamethasone	0 (0)	1 (1.4)
Methylprednisolone	11 (15.5)	9 (12.5)
Prednisolone	9 (12.7)	9 (12.5)
Prednisone	4 (5.6)	6 (8.3)
Concomitant treatments during the study	ND	ND

a. From Week 6 onwards, all patients who were taking oral corticosteroids at the start of the study had to start dose reduction up to the discontinuation of the corticosteroids, unless this was not possible for medical reasons.

n: number of patients with concomitant therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; UC: ulcerative colitis

The proportion of patients receiving concomitant treatment with aminosalicylates and/or corticosteroids at the start of the study, as well as the choice of drugs within these classes, was balanced between the study arms. The company does not provide any information on concomitant therapy during the study.

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: guselkumab vs. golimumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
VEGA	Yes	Yes	Yes	Yes	No[a]	Yes	High
a. The SAP for the VEGA study was possibly prepared with knowledge of the data.							
RCT: randomized controlled trial; SAP: statistical analysis plan							

The risk of bias across outcomes was rated as high for the VEGA study. The reason for this is the preparation of the SAP, which may have been done with knowledge of the data.

Transferability of the study results to the German health care context

The company states that the VEGA study is a global study conducted at 54 study centres in 9 countries. The region with the highest proportion of included study participants is Eastern Europe (here: Poland, Russia, Ukraine). Study centres in Germany, the USA and Australia fell into the "Rest of the world" category. According to the company, more than 90% of study participants in the guselkumab arm and the golimumab arm of the VEGA study were white. According to the company, the inclusion and exclusion criteria of the studies with regard to disease activity parameters (based on the Mayo score) as well as prior and concomitant therapies set a narrow framework based on generally accepted criteria that are common for studies in this therapeutic indication and would also be valid in the German health care context. This ensures that the participants included in the VEGA study adequately represent the target population in the German health care context and that the results are transferable. The company further states that the subgroup analyses for the characteristic "region" did not suggest any relevant effect modification. Pursuant to the company, based on the data from the German health care context, the dosing regimen of golimumab 100 mg every 4 weeks in the maintenance therapy of the comparator arm of the VEGA study adequately reflects the health care situation for all study participants. Overall, the dosage regimen used for the maintenance therapy thus represents an adequate comparator for the benefit assessment of guselkumab in the therapeutic indication of moderate to severe ulcerative colitis. Overall, the company assumes that there are no indications of relevant deviations of the patient populations from 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 3.2.2.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - symptomatic remission
  - bowel symptoms, recorded using the IBDQ subscore of bowel symptoms
  - systemic symptoms, recorded using the IBDQ subscore of systemic symptoms
  - symptoms, recorded using the PGIC
  - fatigue, recorded using the PROMIS Fatigue SF7a
- Health-related quality of life
  - recorded by IBDQ
  - recorded by PROMIS-29
- Side effects
  - serious SAEs
  - discontinuation due to AEs39
  - infections, operationalized as infections and infestations (System Organ Class [SOC], AEs)
  - other specific AEs, if any

The patient-relevant outcomes selected deviate from those selected by the company, which used additional outcomes in its dossier (Module 4C).

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

Table 11: Matrix of outcomes – RCT, direct comparison: guselkumab vs. golimumab

Study	Outcomes									
	All-cause mortality[a]	Symptomatic remission	Bowel symptoms, systemic symptoms (IBDQ)	Symptoms (PGIC)	Fatigue (PROMIS Fatigue SF7a)	Health-related quality of life (IBDQ, PROMIS-29)	SAEs	Discontinuation due to AEs	Infections[b]	Other specific AEs
VEGA	Yes	No[c]	Yes	Yes	Yes	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 reasoning, see Section I 3.2.1 of this dossier assessment.
d. No specific AEs were identified based on the AEs which occurred in the relevant study.

AE: adverse event, IBDQ: Inflammatory Bowel Disease Questionnaire; PGIC: Patient Global Impression of Change; PROMIS: Patient-Reported Outcome Measurement Information System; RCT: randomized controlled trial; SF7a: Short Form 7a; SAE: serious adverse event; SOC: System Organ Class

Morbidity

Symptomatic remission

In the VEGA study, the primary outcome clinical response at Week 12 was recorded by an improvement in the Mayo score. The Mayo score consists of four subscores and includes the patient-reported scales stool frequency (SF) and RB, an endoscopic examination and an assessment of the global health status of the patients by the attending physician. In this context, the endoscopic subscore, based on an imaging procedure, is not per se relevant to the patient, as morbidity is not primarily recorded on the basis of disease symptoms. The subscore assessment of the global health status is also irrelevant to patients, as this assessment is not patient-reported. The Mayo score (as total score) is not considered relevant to patients due to the endoscopic subscore and the subscore for assessing the global health status.

In Module 4C, the company presents the outcome symptomatic remission, based on 2 subscores of the Mayo score. The two scales are the SF and the RB. To meet the criteria for symptomatic remission, patients had to have an SF score of 0 or 1 at Week 38 and no deterioration in SF compared to baseline, and in addition, an RB score of 0 had to be achieved at Week 38. An SF score of 0 or 1 points to a normal number of stools or 1 to 2 stools more than normal, whereby a normal number of stools within 24 hours refers to the patient-

reported individual number of stools in the situation prior to the disease or during disease remission. An RB score of 0 means no blood is visible in the stool. The response thresholds used by the company for SF and RB are appropriate and reflect the recommendations of the FDA and EMA [12,13]. Both symptoms were recorded by patients in a patient diary during the seven days prior to the study visit. The mean value of the three most recent consecutive days was used for the assessment. If less consecutive recordings were available, these were supplemented by the timely closest non-consecutive values within the 7-day period. If less than 3 days were reported in total, the score could not be calculated and the value is missing. The company did not provide any information on how many patients had non-consecutive values taken into account for the determination of the RB or SF scores, or how many patients had missing values for the respective score.

The operationalization of symptomatic remission presented by the company is not suitable for assessing the added benefit in the context of the benefit assessment, as it remains unclear why relevant aspects of the symptoms, in particular abdominal pain, are not included. In principle, it is considered appropriate that both the SF score and the RB score had to be normalized in order to achieve remission. However, since the complete Mayo score includes a medical assessment of the patient's global health status, including e.g. abdominal pain besides the patient-reported symptoms SF and RB, it does not seem appropriate that, as in projects in the field of Crohn's disease, abdominal pain is not additionally recorded as a further key symptom for the assessment of remission as a directly patient-reported outcome.

In addition, from the perspective of avoiding long-term side effects, steroid freedom at Week 38 should also be a criterion in the outcome definition or at least be recorded as a separate outcome (without combining it with imaging procedures or the global assessment of patients by the investigator). Patients should have been steroid-free for a relevant period of time and not just at a single point in time. It is assumed that, upon achieving symptomatic remission without the use of corticosteroids or while adhering to, for example, a 3-month waiting period (see dossier assessment A25-42 [14]), corticosteroid-induced side effects are avoided to a relevant extent and a more stable therapeutic effect is achieved. Based on the dose reduction scheme used in the VEGA study to taper corticosteroids, it was assumed that corticosteroid-free symptomatic remission was generally achievable for most patients in the VEGA study.

In Module 4C, the company did not present such operationalization for the outcome symptomatic remission. Accordingly, no suitable data are available for the benefit assessment for the outcome symptomatic remission. The outcome symptomatic remission in the company’s operationalization is presented as supplementary information in I Appendix B. Regardless of the limitations described above, there were no statistically significant effects.

Mucosal healing

The outcome mucosal healing presented by the company is based on the endoscopy subcomponent of the Mayo score and comprises the proportion of patients with an endoscopy score of 0 or 1 ('normal or inactive disease' or 'mild disease [erythema, reduced vascular pattern, mild friability]') without friability at Week 38. The endoscopy subcomponent of the Mayo score is primarily used to record asymptomatic findings that are not immediately relevant to the patient. Findings identified solely through imaging procedures are not per se relevant to the patient, since morbidity is not primarily recorded on the basis of disease symptoms. It remains unclear to what extent endoscopic assessment can be used as a surrogate for morbidity, and for which patient-relevant outcome mucosal healing represents a surrogate. The company has not presented any surrogate validation in the dossier. The outcome mucosal healing is therefore not included in the benefit assessment.

PGIC

The PGIC scale consists of a single question that the patients could use to assess the changes in the symptoms of UC. Using PGIC, patients were asked to assess the change in disease severity on a 7-point scale ('very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse', 'very much worse') in relation to the start of the study.

According to the SAP, analyses on improvement by ≥ 1 point and analyses on improvement by ≥ 2 points were defined. For the PGIC, the company presented responder analyses for both analyses in Module 4C. As the patients included in the VEGA study were symptomatic at the start of the study (ulcerative colitis of at least moderate severity with a Mayo score of ≥ 6) and treatment with guselkumab can therefore, in principle, lead to an improvement in symptoms, responder analyses focusing on improvement are generally considered appropriate for the benefit assessment. The analysis presented by the company in Module 4C on the proportion of patients showing an improvement by ≥ 1 point (response categories 'slightly improved' to 'very much improved') is used to derive the added benefit, as it is assumed that, in the present situation, any improvement represents a change that is noticeable to the patient.

Hospitalization due to ulcerative colitis/visits to the emergency department/surgeries

The company provides analyses on hospitalizations, visits to the emergency department and surgeries due to ulcerative colitis. Hospitalization due to events related to ulcerative colitis can generally serve as a suitable operationalization for reflecting severe symptoms of ulcerative colitis. However, as no further details are available regarding the operationalization and the underlying events (for example, in the form of a list of preferred terms [PTs] in accordance with the Medical Dictionary for Regulatory Activities [MedDRA]), the analyses relating to hospitalization, admissions to the emergency department and surgeries due to ulcerative colitis-related events are not used in this benefit assessment.

The outcome hospitalization for any cause is also not shown. It should be noted here that data on the hospitalization were recorded up to 16 weeks after discontinuation of treatment and were to be included in the analysis. It is therefore possible that data relating to subsequent therapies are also included in the analysis, although it remains unclear whether hospitalizations may also have taken place to initiate subsequent therapies. Data on subsequent therapies performed after treatment discontinuation are not available. The results for the outcome hospitalization due to any cause cannot be meaningfully interpreted and are therefore not presented. Regardless of this, the analysis reveals no statistically significant effect.

Health-related quality of life and morbidity

IBDQ total score as well as bowel symptoms and systemic symptoms (IBDQ symptom scales)

For health-related quality of life, the company presented analyses on the IBDQ total score and on the PROMIS-29 (see below), with the IBDQ also including symptom scales for bowel symptoms and systemic symptoms. As response criteria, the company used the post-hoc defined threshold values of an improvement by ≥ 28.8 points for the IBDQ total score, ≥ 9 points for bowel symptoms and ≥ 4.5 points for systemic symptoms, each of which corresponds to ≥ 15% of the scale range. As the patients included in the VEGA study were symptomatic at the start of the study (ulcerative colitis of at least moderate severity with a Mayo score of ≥ 6) and treatment with guselkumab can therefore, in principle, lead to an improvement in symptoms, responder analyses focusing on improvement are generally considered appropriate for the benefit assessment. 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 IBDQ symptom scales comprise 10 questions on bowel symptoms and 5 questions on systemic symptoms, and cover patient-relevant aspects of the disease that are not captured by other outcomes in the present data situation. 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.

Outcomes recorded using the PROMIS

PROMIS is a valid, generic system consisting of domain-specific instruments for the self-reported and proxy-reported assessment of physical, mental, and social health. The VEGA study used the following patient-reported PROMIS questionnaires: PROMIS-29 v2.0 to record

the health-related quality of life, and PROMIS Fatigue SF7a to record fatigue. As the patients included in the VEGA study were symptomatic at the start of the study (ulcerative colitis of at least moderate severity with a Mayo score of ≥ 6) and treatment with guselkumab can therefore, in principle, lead to an improvement in symptoms, responder analyses focusing on improvement are generally considered appropriate for the benefit assessment.

Fatigue (PROMIS Fatigue SF7a)

The PROMIS Fatigue SF7a is a generic questionnaire designed to record fatigue across indications. The questionnaire comprises a total of 7 items. It is recommended by the PROMIS Manual as the preferred choice among the available PROMIS questionnaires for self-reported assessment of fatigue in adults and was designed to cover the full spectrum of fatigue severity [15,16]. This is a comprehensively validated instrument, the validity of which in the present therapeutic indication was investigated among other things [17]. The PROMIS Fatigue SF7a is therefore used to assess the outcome fatigue in this benefit assessment.

In Module 4C of its dossier, the company presents responder analyses on the post hoc defined response criterion of an improvement of ≥ 8.07 points for the PROMIS Fatigue SF7a. 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 score range for the PROMIS Fatigue SF7a is 29.4 to 83.2 [15], resulting in a scale span of 53.8. The response criterion of 8.07 points, applied post hoc, corresponds to exactly 15% of this scale span; consequently, the responder analyses presented by the company comply with the stipulations set out in the Methods paper and are used for the benefit assessment.

PROMIS-29

The PROMIS-29 is a generic questionnaire designed to assess health-related quality of life across indications. The questionnaire comprises a total of 29 items from the PROMIS questionnaire system and is composed of seven domain-specific short-form questionnaires, each containing four items and a numerical rating scale (NRS) for pain intensity.

According to the PROMIS Manual, the results of PROMIS-29 v2.0 can be presented either in the form of seven domain scores plus NRS, or as two component summaries: PCS and MCS. Both component summaries incorporate all seven domains and the NRS, albeit with different weightings [18,19]. For both component summaries, a high value corresponds to a better health-related quality of life.

Continuous analyses of the seven domain scores and the NRS for pain intensity were prespecified in the VEGA study protocol. In addition, the SAP – which, however, was not created before approximately three months after the second data cut-off (see Section I 3.1.2)

– described responder analyses on an improvement of ≥ 5 points compared to baseline. In addition, the study report includes post-hoc responder analyses on the improvement of ≥ 3 points from baseline. In cases where the response criterion defined in the SAP (≥ 5 points) does not correspond to ≥ 15% of the scale range, the company calculated post-hoc responder analyses for the benefit assessment using a response criterion of exactly 15% of the scale range. For the VEGA study, the company did not present any analyses of the PROMIS-29 in the form of the PCS and the MCS in its dossier. However, in the current data situation, which includes results for the seven domain scores and the NRS of the PROMIS-29, analyses of the component summaries appear, in principle, possible and provide a more comprehensive picture of health-related quality of life than a separate consideration of the individual domains. However, according to the PROMIS-29 manual, consideration of the individual domains also represents an appropriate analysis. Therefore, in the current data situation, the analysis of the seven domain scores—as prespecified in the study protocol—were used for the benefit assessment together with the NRS for pain intensity and the analyses presented by the company in Module 4C.

Manual conversion of raw values into T-scores is appropriate in this situation

In accordance with the relevant PROMIS manuals [15,16], the raw values from the respective instrument must be converted into T-scores for analysis. Two types of scoring are described for this purpose: a so-called "Response Scoring Pattern", which can be calculated online via the HealthMeasures Scoring Service [20] and free of charge via tools. It uses the respective item-level parameters for each item and each answer. Alternatively, a manual conversion of the raw value into a T-Score is possible. For this purpose, PROMIS provides online conversion tables for all short forms. Both manual scoring using conversion tables and the use of the 'Response Scoring Pattern' via the HealthMeasures Scoring Service utilize T-scoring. According to the PROMIS manuals, the use of the "Response Scoring Pattern" should be favoured, as it measures more accurately and deals better with missing values for individual items. According to the company, the raw values were converted to T-scores manually using the conversion tables provided in the PROMIS manuals. According to company, the advantage of the tool provided online by the HealthMeasures Scoring Service—namely, that it handles missing values more effectively—is not relevant in this case, as all PROMIS questionnaires in the VEGA study were completed using a digital tool that does not allow individual items to be skipped. Therefore, there are no missing values at the level of individual items as per the company. The company's reasoning is comprehensible, and it is therefore assumed that the manual conversion of the raw values into T-scores instead of the use of 'response pattern scoring', will have no impact in this situation.

Side effects

Recording of disease-related events

The company presented analyses both with and without disease-related events for the outcomes AEs, SAEs and discontinuations due to AEs. In the VEGA study, AEs were classified as disease-related events using a Preferred Term (PT) list. In addition to PTs clearly related to ulcerative colitis (such as the PT 'ulcerative colitis'), the list also included PTs with no clear relation to the disease. For example, the PTs nausea, vomiting or flatulence may occur independently of ulcerative colitis or may be side effects. However, as the majority of disease-related events in the overall rates of the side effects outcomes were attributable to the PT ulcerative colitis, the overall rates excluding disease-related events are used for this benefit assessment.

Operationalization of the outcome infections

In the VEGA study, the outcome infections was a prespecified adverse event of special interest and was recorded by the investigator in the electronic case report form as 'infections' and 'serious infections'. The operationalization of the outcome as infections and infestations (SOC, AEs) according to MedDRA was used for the benefit assessment.

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

I 3.2.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: guselkumab versus golimumab

Study	Study level	Outcomes									
		All-cause mortality[a]	Symptomatic remission	Bowel symptoms, systemic symptoms (IBDQ)	Symptoms (PGIC)	Fatigue (PROMIS Fatigue SF-7a)	Health-related quality of life (IBDQ, PROMIS-29)	SAEs	Discontinuation due to AEs	Infections[b]	Other specific AEs
VEGA	H[c]	H[d]	–[e]	H[f]	H[f]	H[f]	H[f]	H[d]	H	H[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. High risk of bias across outcomes. This leads to a high risk of bias for each outcome.
d. Incomplete observations for potentially informative reasons.
e. No suitable data available; for reasoning, see Section I 3.2.1 of this dossier assessment.
f. Due to the high proportion of values imputed by non-responder imputation.

AE: adverse event; H: high; IBDQ: Inflammatory Bowel Disease Questionnaire; PGIC: Patient Global Impression of Change; PROMIS: Patient-Reported Outcome Measurement Information System; RCT: randomized controlled trial; SF7a: Short Form 7a; SAE: serious adverse event; SOC: System Organ Class

The risk of bias across outcomes was rated high, as the SAP may have been prepared with knowledge of the data (see Section I 3.2.1). This led to a high risk of bias for the results of all outcomes.

No suitable data are available for the outcome symptomatic remission (see Section I 3.2.1), therefore, the risk of bias for this outcome is not assessed.

In the VEGA study, 6 patients in the intervention arm (8.5%) and 13 patients in the control arm (18.1%) discontinued the study medication prematurely. Consequently, the results for the outcomes of all-cause mortality and side effects are based on an incomplete observation period for potentially informative reasons.

The company uses non-responder imputation (NRI) to impute missing values in the responder analyses of the morbidity and health-related quality of life scales. In the VEGA study, missing values for a total of 6 patients in the intervention arm (8.5%) and 15 patients in the control arm (20.8%) were imputed using NRI. The company's underlying assumption that no event was to be expected in patients without value at Week 48 could not be sufficiently verified.

Overall, the analyses based on NRI were subject to uncertainty due to the high proportion of missing values.

Summary assessment of the certainty of conclusions

In addition to the high risk of bias across outcomes and the high outcome-specific risk of bias, the following uncertainty exists for the results of the VEGA study (as described in Section I 3.1.2), which has an impact on the certainty of conclusions:

- administration of study medication in the intervention and control arms not fully compliant with the SmPC

Overall, due to the mentioned uncertainties in the VEGA study, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

I 3.2.3 Results

Table 13 summarizes the results of the comparison of guselkumab with golimumab in adults with moderately to severely active ulcerative colitis 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.

The results on common AEs, common SAEs and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: guselkumab vs. golimumab (multipage table)

Study outcome category outcome	Guselkumab		Golimumab		Guselkumab vs. golimumab
	L	patients with event n (%)	L	patients with event n (%)	RR [95% CI]; p-value[a]
VEGA					
Mortality (until Week 50)					
All-cause mortality[b]	71	1 (1.4)	72	0 (0)	–
Morbidity (at Week 38)					
Symptomatic remission	No suitable data[c]				
Bowel symptoms (IBDQ – improvement[d])	71	53 (74.6)	72	43 (59.7)	1.25 [0.99; 1.58]; 0.060
Systemic symptoms (IBDQ – improvement[d])	71	50 (70.4)	72	40 (55.6)	1.27 [0.98; 1.64]; 0.069
Fatigue (PROMIS Fatigue SF 7a – improvement[e])	71	34 (47.9)	72	27 (37.5)	1.28 [0.87; 1.88]; 0.213
Symptoms (PGIC – improvement[f])	71	63 (88.7)	72	53 (73.6)	1.21 [1.03; 1.42]; 0.023

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: guselkumab vs. golimumab (multipage table)

Study outcome category outcome	Guselkumab L	Guselkumab patients with event n (%)	Golimumab L	Golimumab patients with event n (%)	Guselkumab vs. golimumab RR [95% CI]; p-value[a]
Health-related quality of life (at Week 38)					
IBDQ total score – (improvement)[d]	71	52 (73.2)	72	43 (59.7)	1.23 [0.97; 1.55]; 0.089
Bowel symptoms	71	53 (74.6)	72	43 (59.7)	1.25 [0.99; 1.58]; –
Systemic symptoms	71	50 (70.4)	72	40 (55.6)	1.27 [0.98; 1.64]; –
Emotional functioning	71	49 (69.0)	72	43 (59.7)	1.16 [0.90; 1.48]; –
Social functioning	71	53 (74.6)	72	44 (61.1)	1.22 [0.97; 1.54]; –
PROMIS-29 – improvement					
Physical Component Summary (PCS)				ND	
Mental Component Summary (MCS)				ND	
Physical functioning[g]	71	36 (50.7)	72	31 (43.1)	1.18 [0.83; 1.68]; 0.364
Anxiety[h]	71	38 (53.5)	72	32 (44.4)	1.20 [0.86; 1.69]; 0.281
Depression[h]	71	33 (46.5)	72	29 (40.3)	1.15 [0.79; 1.67]; 0.457
Exhaustion[h]	71	36 (50.7)	72	29 (40.3)	1.26 [0.88; 1.81]; 0.215
Sleep interference[h]	71	34 (47.9)	72	22 (30.6)	1.56 [1.03; 2.39]; 0.038
Participation in social roles and activities[g]	71	48 (67.6)	72	36 (50.0)	1.35 [1.02; 1.79]; 0.036
Pain interference[h]	71	43 (60.6)	72	36 (50.0)	1.21 [0.90; 1.63]; 0.208
Pain intensity[h]	71	20 (28.2)	72	17 (23.6)	1.19 [0.68; 2.07]; 0.538
Side effects (until Week 50)[i]					
AEs (supplementary information)	71	45 (63.4)	72	46 (63.9)	–
SAEs	71	4 (5.6)	72	3 (4.2)	1.36 [0.32; 5.83]; 0.682
Discontinuation due to AEs	71	1 (1.4)	72	1 (1.4)	1.01 [0.06; 15.91]; 0.993
Infections[j]	71	17 (23.9)	72	23 (31.9)	0.75 [0.44; 1.28]; 0.287

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: guselkumab vs. golimumab (multipage table)

Study outcome category outcome	Guselkumab L patients with event n (%)	Golimumab L patients with event n (%)	Guselkumab vs. golimumab RR [95% CI]; p-value[a]
a. Cochran-Mantel-Haenszel method with the stratification factor corticosteroid treatment at baseline (yes/no). Missing values are taken into account using NRI (for outcomes on morbidity and health-related quality of life). b. The results on all-cause mortality are based on the data on fatal AEs. c. See Section I 3.2.1 of this dossier assessment for the reasoning. d. An increase in the score by ≥ 15% of the scale range (total score: ≥ 28.8 points; bowel symptoms: ≥ 9 points; systemic symptoms or social functioning: ≥ 4.5 points; or emotional functioning: ≥ 10.8 points) compared to baseline is considered a clinically relevant improvement (scale ranges: 32 to 224 [total score], 10 to 70 [bowel symptoms], 5 to 35 [systemic symptoms and social functioning] or 12 to 84 [emotional functioning]). e. A score decrease by ≥ 8.07 points from baseline is considered a clinically relevant improvement (scale range: 29.4 to 83.2). f. Defined as any improvement in the symptom severity compared to the start of the study ("very much improved", "much improved" or "slightly improved"). g. An increase in the score by ≥ 15% of the scale range (physical functioning: ≥ 5.1 points; participation in social roles and activities: ≥ 5.51 points) compared to baseline is considered a clinically relevant improvement (scale ranges: 22.9 to 56.9 [physical functioning]; 27.5 to 64.2 [participation in social roles and activities]). h. A score decrease by 15% of the scale range (anxiety: ≥ 6.2 points; depression: ≥ 5.76 points; exhaustion: ≥ 6.32 points; sleep interference: ≥ 6.2 points; pain interference: ≥ 5.1 points; pain intensity: ≥ 5 points) from baseline is considered a clinically relevant improvement (scale ranges: 40.3 to 81.6 [anxiety]; 41.0 to 79.4 [depression]; 33.7 to 75.8 [exhaustion]; 32.0 to 73.3 [sleep interference]; 41.6 to 75.6 [pain interference]; 0 to 10 [pain intensity]). i. Overall rate excluding disease-related events (see Section I 3.2.1 of this dossier assessment for explanation). j. Operationalized as infections and infestations (SOC, AEs). AE: adverse event; CI: confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary Score; ND: no data; n: number of patients with (at least one) event; N: number of analysed patients; NRI: non-responder imputation; PHS: Physical Health Score; PGIC: Patient Global Impression of Change; PROMIS: Patient-Reported Outcome Measurement Information System; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF7a: Short Form 7a; SOC: System Organ Class		

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

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 guselkumab in comparison with golimumab; an added benefit is therefore not proven.

Morbidity

Symptomatic remission

No suitable data are available for the outcome symptomatic remission (see Section I 3.2.1 for reasoning). There was no hint of an added benefit of guselkumab in comparison with golimumab; an added benefit is therefore not proven.

Bowel symptoms (IBDQ), systemic symptoms (IBDQ), fatigue (PROMIS Fatigue SF7a)

There was no statistically significant difference between the treatment groups for the outcomes bowel symptoms (recorded using the IBDQ), systemic symptoms (recorded using the IBDQ) and fatigue (recorded using PROMIS-Fatigue SF7a). There was no hint of an added benefit of guselkumab over golimumab; an added benefit is therefore not proven.

PGIC

A statistically significant difference between the treatment groups in favour of guselkumab was shown for the outcome of PGIC. The difference, however, is no more than marginal for this outcome of the category non-serious/non-severe symptoms/late complications. There was no hint of an added benefit of guselkumab in comparison with golimumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

No statistically significant difference between treatment groups was found for the outcome health-related quality of life (recorded using the IBDQ total score). There was no hint of an added benefit of guselkumab in comparison with golimumab; an added benefit is therefore not proven.

PROMIS-29

No data were available for the PCS and the MCS of the PROMIS-29. There was no hint of an added benefit of guselkumab over golimumab; an added benefit is therefore not proven.

Physical functioning, anxiety, depression, exhaustion, pain interference and pain intensity

No statistically significant differences between the treatment groups were found for the domains physical functioning, anxiety, depression, exhaustion, pain interference and pain intensity. There was no hint of an added benefit of guselkumab over golimumab; an added benefit is therefore not proven.

Sleep interference and participation in social roles and activities

For the domains sleep interference and participation in social roles and activities, there is a statistically significant difference in favour of guselkumab in comparison with golimumab. In

each case, this results in a hint of an added benefit of guselkumab in comparison with golimumab.

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). Consequently, there is no hint of greater or lesser harm from guselkumab in comparison with golimumab for either of them; greater or lesser harm is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

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

- Age (≤ median age vs. > median age)
- Sex (female versus male)
- Severity of ulcerative colitis (moderately active vs. severely active)

For the item severity of ulcerative colitis, moderately active disease was defined as a Mayo score of ≥ 6 but ≤ 10. Severely active disease was defined as a Mayo score > 10.

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

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

It is not possible to assess the impact of incompletely observed patients or values imputed using NRI on subgroup effects or interaction tests. Due to the high proportions in each case, the subgroup analyses cannot be interpreted. Furthermore, when applying the method described above there are not effect modifications based on the analyses presented by the company.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the 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 3.3.1 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 3.2 (see Table 14).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Symptoms (PGIC)

No sufficient information is available for the classification of the severity grade for the outcome symptoms (recorded with the PGIC) that would allow a classification as serious/severe. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 14: Extent of added benefit at outcome level: guselkumab versus golimumab (multipage table)

Outcome category **outcome**	**Guselkumab vs. golimumab** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.4 vs. 0 RR: NC; p = NC	Lesser benefit/added benefit not proven
Morbidity		
Symptomatic remission	No suitable data[c]	Lesser benefit/added benefit not proven
Bowel symptoms (IBDQ – improvement)	74.6 vs. 59.7 RR: 1.25 [0.99; 1.58]; p = 0.060	Lesser benefit/added benefit not proven
Systemic symptoms (IBDQ – improvement)	70.4 vs. 55.6 RR: 1.27 [0.98; 1.64]; p = 0.069	Lesser benefit/added benefit not proven
Fatigue (PROMIS Fatigue SF 7a – improvement)	47.9 vs. 37.5 RR: 1.28 [0.87; 1.88]; p = 0.213	Lesser benefit/added benefit not proven
PGIC (improvement)	88.7 vs. 73.6 RR: 1.21 [1.03; 1.42]; RR: 0.83 [0.70; 0.97][d]; p = 0.023 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Health-related quality of life		
IBDQ total score (improvement)	73.2 vs. 59.7 RR: 1.23 [0.97; 1.55]; p = 0.089	Lesser benefit/added benefit not proven
PROMIS-29 Physical Component Summary (PCS – improvement)	ND vs. ND RR: NC; p = NC	Lesser benefit/added benefit not proven
PROMIS-29 Mental Component Summary (MCS - improvement)	ND vs. ND RR: NC; p = NC	Lesser benefit/added benefit not proven
PROMIS-29 physical functioning (improvement)	50.7 vs. 43.1 RR: 1.18 [0.83; 1.68]; p = 0.364	Lesser benefit/added benefit not proven
PROMIS-29 Anxiety (improvement)	53.5 vs. 44.4 RR: 1.20 [0.86; 1.69]; p = 0.281	Lesser benefit/added benefit not proven

Table 14: Extent of added benefit at outcome level: guselkumab versus golimumab (multipage table)

Outcome category **outcome**	**Guselkumab vs. golimumab** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
PROMIS-29 Depression (improvement)	46.5 vs. 40.3 RR: 1.15 [0.79; 1.67]; p = 0.457	Lesser benefit/added benefit not proven
PROMIS-29 Fatigue (improvement)	50.7 vs. 40.3 RR: 1.26 [0.88; 1.81]; p = 0.215	Lesser benefit/added benefit not proven
PROMIS-29 Sleep interference (improvement)	47.9 vs. 30.6 RR: 1.56 [1.03; 2.39]; RR: 0.64 [0.42; 0.97][d]; p = 0.038 probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
PROMIS-29: participation in social roles and activities (improvement)	67.6 vs. 50.0 RR: 1.35 [1.02; 1.79]; RR: 0.74 [0.56; 0.98][d]; p = 0.036 probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
PROMIS-29 Pain interference (improvement)	60.6 vs. 50.0 RR: 1.21 [0.90; 1.63]; p = 0.208	Lesser benefit/added benefit not proven
PROMIS-29 Pain Intensity (Improvement)	28.2 vs. 23.6 RR: 1.19 [0.68; 2.07]; p = 0.538	Lesser benefit/added benefit not proven
Side effects		
SAEs	5.6 vs. 4.2 RR: 1.36 [0.32; 5.83]; p = 0.682	Greater/lesser harm not proven
Discontinuation due to AEs	1.4 vs. 1.4 RR: 1.01 [0.06; 15.91]; p = 0.993	Greater/lesser harm not proven
Infections (AEs)	23.9 vs. 31.9 RR: 0.75 [0.44; 1.28]; p = 0.287	Greater/lesser harm not proven

Table 14: Extent of added benefit at outcome level: guselkumab versus golimumab (multipage table)

Outcome category **outcome**	**Guselkumab vs. golimumab** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. See Section I 3.2.1 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; CI: confidence interval; CI_u: upper limit of the confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary Score; NC: not calculated; ND: no data; PGIC: Patient Global Impression of Change; PHS: Physical Health Score; PROMIS: Patient-reported Outcome Measurement Information System; RR: relative risk; SF7a: Short Form 7a; SAE: serious adverse event		

I 3.3.2 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 guselkumab in comparison with golimumab

Positive effects	**Negative effects**
Health-related quality of life ▪ sleep interference, participation in social roles and activities (PROMIS-29 in each case): hint of added benefit – extent: "minor"	–
No suitable data are available for the outcomes symptomatic remission, PCS (PROMIS-29) and MCS (PROMIS-29).	
PROMIS: Patient-Reported Outcome Measurement Information System	

For research question 1 of this benefit assessment, guselkumab shows positive effects compared to golimumab in the domains sleep interference and participation in social roles and activities of the PROMIS-29. In this dossier, the company has not submitted the PCS and the MCS of the PROMIS-29. The observed positive effects of guselkumab in the two individual domains of the PROMIS-29 only reflect partial aspects of health-related quality of life. Overall, however, these effects are not sufficient to justify the derivation of a minor added benefit for the comprehensive concept of health-related quality of life in the present data situation.

In summary, there is no hint of an added benefit of guselkumab versus the ACT for patients 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 deviates from that of the company, which derived an indication of considerable added benefit for this research question.

I 4 Research question 2: patients who are not eligible for a biologic agent

I 4.1 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 guselkumab (status: 16 April 2025)
- Bibliographical literature search on guselkumab (last search on 16 April 2025)
- Search in trial registries/trial results databases for studies on guselkumab (last search on 16 April 2025)
- Search on the G-BA website for etrasimod (last search on 16 April 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on guselkumab (last search on 12 June 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company's findings, the check of completeness of the study pool did not identify any study for a direct comparison of guselkumab with the ACT for research question 2.

In Module 4C, the company describes the pivotal studies QUASAR Induction Study 1, QUASAR Induction Study 2 and QUASAR Maintenance Study as supportive information to assess the efficacy and tolerability of guselkumab [21,22]. All three studies were conducted under a single protocol. This study compared guselkumab with placebo. Patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or a new therapy were included. A comparison versus the ACT is not available. The company did not claim an added benefit. Concurring with the company's approach, the QUASAR studies were not used for the benefit assessment.

I 4.2 Results on added benefit

The company did not present any suitable data for assessing the added benefit of guselkumab compared with the ACT in adult patients who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist, integrin inhibitor or interleukin inhibitor). There is no hint of an added benefit of guselkumab in comparison with the ACT; an added benefit is therefore not proven for this research question.

I 4.3 Probability and extent of added benefit

The company has not provided any suitable data to assess the added benefit of guselkumab compared with the ACT in adult patients who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist, integrin inhibitor or interleukin inhibitor). An added benefit of guselkumab in comparison with the ACT is therefore not proven for research question 2.

This concurs with the company's assessment.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of guselkumab in comparison with the ACT is summarized in Table 16.

Table 16: Guselkumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b, c]	Probability and extent of added benefit
Adults with moderately to severely active ulcerative colitis[d]			
1	Patients who have had an inadequate response to, lost response to, or are intolerant to conventional therapy	Adalimumab or golimumab or infliximab or mirikizumab or ozanimod or ustekinumab or vedolizumab	Added benefit not proven
2	Patients 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 filgotinib or golimumab or infliximab or mirikizumab or ozanimod or tofacitinib or upadacitinib or ustekinumab or vedolizumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Switching within or between drug classes is permitted. Any potential dose adjustment options are assumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.
c. Guselkumab is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
e. If infliximab is used, it should be combined with a thiopurine, if necessary.

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 6 References for English extract

Please see full dossier assessment for full reference list.

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

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