Guselkumab
(Crohn’s disease)

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

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

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I List of abbreviations

Abbreviation	Meaning
6-MP	6-mercaptopurine
ACT	appropriate comparator therapy
AE	adverse event
AZA	azathioprine
CDAI	Crohn’s Disease Activity Index
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)
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NRI	non-responder imputation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SES-CD	Simple Endoscopic Score for Crohn’s Disease
SF	stool frequency
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
SOC	Special Organ Class
TNF	tumour necrosis factor
WPAI-CD	Work Productivity and Activity Impairment Questionnaire – Crohn’s Disease

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent (tumour necrosis factor [TNF]α antagonist or integrin inhibitor or interleukin inhibitor).

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

Table 2: Research questions of the benefit assessment of guselkumab

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

a. Presented 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. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
c. Continuation of an inadequate therapy does not concur with the specified ACT.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

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

Study pool and study design

The GALAXI studies were used for both research questions of the benefit assessment. These are double-blind, multicentre RCTs comparing guselkumab at various doses with ustekinumab and placebo in adults with moderately to severely active Crohn's disease. The initial diagnosis of Crohn's disease must have been established at least 3 months before enrolment.

For this benefit assessment, it is assumed on the basis of the inclusion criteria that patients in the GALAXI studies had moderately to severely active Crohn's disease.

To be eligible for study participation, patients had to have received at least one conventional therapy (i.e. corticosteroids, immunosuppressants) or at least one treatment with biologics (e.g. TNFα antagonist or integrin inhibitor).

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

- Inadequate response with or intolerance to
  - corticosteroids (including prednisone, budesonide and beclomethasone dipropionate) or
  - immunosuppressants azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (MTX)
- Corticosteroid-dependent disease (i.e. corticosteroids cannot be discontinued without the symptoms of Crohn's disease returning)

Patients may already have received biologic therapy (i.e. a TNF antagonist or vedolizumab) without, however, having shown any intolerance or an inadequate response.

Non-eligibility for treatment with biologics was defined as primary non-response (i.e. no initial response) or secondary non-response (i.e. loss of response whilst on continuous treatment) or intolerance to at least one biologic therapy (i.e. adalimumab, infliximab, certolizumab pegol, vedolizumab).

In the 5-arm GALAXI 1 study, a total of 360 patients were randomly allocated in a 1:1:1:1:1 ratio to treatment with guselkumab in three different dosages (each study arm N = 73), ustekinumab (N = 71) or placebo (N = 70). The sub-populations relevant to research questions 1 and 2, comprising patients unsuitable for conventional therapy and patients unsuitable for biologic therapy respectively, comprise 35 and 38 patients from the guselkumab arm relevant to this benefit assessment, and 30 and 41 patients from the ustekinumab arm.

In the four-arm studies GALAXI 2 and GALAXI 3, a total of 523 and 525 patients were randomized in a 2:2:2:1 ratio to treatment with guselkumab at two different doses (in GALAXI 2, N = 148 per study arm, and in GALAXI 3, N = 151 and N = 148), ustekinumab (N = 150 each) or placebo (N = 77 and N = 76). In the GALAXI 2 study, the sub-populations of patients who were ineligible for conventional therapy or biologics comprised 70 and 79 patients, respectively, in the guselkumab arm relevant to this benefit assessment, and 68 and 82 patients, respectively, in the ustekinumab arm. In the GALAXI 3 study, the subpopulations of patients who were non-responders to conventional therapy and biologics comprised 70 and 78 patients, respectively, in the guselkumab arm relevant to this benefit assessment, and 72 and 78 patients, respectively, in the ustekinumab arm.

The duration of treatment in the studies GALAXI 1, GALAXI 2 and GALAXI 3 was 48 weeks.

The primary outcome in the GALAXI 1 study was the change in CDAI at Week 12. In the studies GALAXI 2 and GALAXI 3, the two co-primary outcomes were:

- CDAI response (defined as a reduction of ≥ 100 points compared with baseline or a CDAI score < 150) at Week 12 and CDAI remission (defined as a CDAI score < 150) at Week 48
- CDAI response at Week 12 and endoscopic response at Week 48

Patient-relevant outcomes of morbidity, health-related quality of life and side effects were additionally recorded.

Relevant limitations of the GALAXI studies

Lack of options for escalating the intervention

From Week 16 onwards, patients in the GALAXI studies received 100 mg of guselkumab subcutaneously every 8 weeks as maintenance therapy, with no option to escalate treatment. However, according to the Summary of Product Characteristics (SmPC), in patients who, in the physician's opinion, do not show sufficient therapeutic benefit following induction treatment, a significantly higher maintenance dose of 200 mg administered as a subcutaneous injection may be considered from Week 12 onwards, and every 4 weeks thereafter. In the GALAXI studies, patients in the relevant intervention arm may therefore have received an insufficient dose of guselkumab.

Comparator therapy not administered in full compliance with the SmPC

Following the induction dose, patients received ustekinumab subcutaneously every 8 weeks. However, the SmPC recommend one dose every 12 weeks. Only patients who lose response to treatment at 12-week intervals may receive the next dose every 8 weeks. In the GALAXI studies, patients in the relevant comparator arm therefore may have been overdosed with ustekinumab.

Lack of independence of the studies GALAXI 2 and GALAXI 3

The studies GALAXI 2 and GALAXI 3 have identical study designs and investigate the same primary and secondary outcomes with the same statistical analysis plan. They are powered separately for the primary outcomes. The joint analysis (i.e. pooling) of GALAXI 2 and GALAXI 3 was prespecified. The studies GALAXI 2 and GALAXI 3 were conducted simultaneously, predominantly at the same study centres. This means that patients were divided between two studies at the same centres, under the supervision of the same investigators. The studies GALAXI 2 and GALAXI 3 are therefore no independent studies. Hereinafter, the term GALAXI 2/3 is used to refer to the pooled data from the studies GALAXI 2 and GALAXI 3. The certainty of conclusions of the results from the pooled GALAXI 2/3 data initially corresponds to that of the results from one study.

Risk of bias

In the GALAXI studies, the results for all outcomes, with the exception of discontinuation due to adverse events (AEs), are subject to a high risk of bias.

For the results on the outcomes in the categories morbidity and health-related quality of life, this is due to the high proportion of values imputed using non-responder imputation (NRI), or the fact that this proportion varies between the arms. With regard to the results for the outcome all-cause mortality and the outcomes in the AE category (excluding discontinuation due to AEs), the reason for the high risk for bias is that, in each case, the data are incomplete for potentially informative reasons, as follow-up observation was discontinued after the end of treatment and is therefore potentially shortened.

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

Summary assessment of the certainty of conclusions

Based on the GALAXI studies, at most hints, e.g. of an added benefit, can be derived for all outcomes presented.

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

Results

Mortality

Overall survival

The results on all-cause mortality were based on data on fatal AEs. There were no deaths in either GALAXI 1 or GALAXI 2/3. There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Corticosteroid-free remission (patient-reported outcome 2 [PRO2]), bowel symptoms (Inflammatory Bowel Disease Questionnaire [IBDQ]), systemic symptoms (IBDQ), absence of fistula, fatigue (Patient-Reported Outcomes Measurement Information System [PROMIS] Fatigue SF7a), symptoms (Patient Global Impression of Change [PGIC], Patient's Global Impression of Severity [PGIS]) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcomes corticosteroid-free remission (recorded using PRO2), bowel symptoms and systemic symptoms (each recorded using the IBDQ), absence of fistula, fatigue (recorded using PROMIS Fatigue SF7a), symptoms (recorded using PGIC and PGIS) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven in each case.

Activity impairment (Work Productivity and Activity Impairment Questionnaire – Crohn's Disease [WPAI-CD Item 6])

No suitable data are available for the outcome activity impairment (recorded using WPAI-CD item 6). There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

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

PROMIS-29 Physical Component Summary (PCS) and Mental Component Summary (PCS)

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using PROMIS-29). There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs and infections (AEs)

There was no statistically significant difference between the treatment groups for any of the outcomes SAEs, discontinuation due to AEs and infections (AEs). Consequently, there is no hint of greater or lesser harm from guselkumab in comparison with ustekinumab 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 (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, neither positive nor negative effects of guselkumab compared with ustekinumab were shown in the relevant subpopulation. In summary, there is no hint of an added benefit of guselkumab over ustekinumab for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy. An added benefit is therefore not proven.

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

Results

Mortality

Overall survival

The results on all-cause mortality are based on data on fatal AEs. There were no deaths in either GALAXI 1 or GALAXI 2/3. There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Corticosteroid-free remission (PRO2)

A statistically significant difference between the treatment groups in favour of guselkumab was found for the outcome corticosteroid-free remission (recorded using PRO2). However, the extent of the effect in this non-serious/non-severe outcome was no more than marginal. There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Bowel symptoms (IBDQ), systemic symptoms (IBDQ), absence of fistula, fatigue (PROMIS Fatigue SF7a), symptoms (PGIC, PGIS) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for each of the outcomes bowel symptoms and systemic symptoms (recorded using the IBDQ), absence of

[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].

fistula, fatigue (recorded using the PROMIS Fatigue SF7a), symptoms (recorded using PGIC and PGIS) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven in each case.

Activity impairment (WPAI-CD Item 6)

No suitable data are available for the outcome activity impairment (recorded using WPAI-CD item 6). There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

A statistically significant difference between the treatment groups in favour of guselkumab was found for health-related quality of life (recorded using the IBDQ). There is a hint of minor added benefit of guselkumab in comparison with golimumab.

PROMIS-29 Physical Health Summary score (PHS) and Mental Health Summary score (MHS)

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using PROMIS-29). There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs and infections (AEs)

There was no statistically significant difference between the treatment groups for any of the outcomes SAEs, discontinuation due to AEs and infections (AEs). Consequently, there is no hint of greater or lesser harm from guselkumab in comparison with ustekinumab 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 2: patients who are not eligible for a biologic agent)

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

For research question 2 of this benefit assessment, a positive effect of guselkumab compared to ustekinumab was shown in the relevant subpopulation. For the outcome health-related quality of life, operationalized as an improvement in the IBDQ total score, there is a hint of added with the extent "minor". In summary, there is a hint of minor added benefit of guselkumab over ustekinumab for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor).

Probability and extent of added benefit – summary

Table 3 shows a summary of probability and extent of the added benefit of guselkumab.

Table 3: Guselkumab – probability and extent of added benefit

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

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. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
c. Continuation of an inadequate therapy does not concur with the specified ACT.
d. The GALAXI studies did not include any patients who had previously been treated with an IL-12/23 or IL-23 drug. An exception was made for patients who had received a minimum amount of ustekinumab at the approved dose and who had both met the required washout criterion and shown no failure of or intolerance to ustekinumab. It remains unclear whether the observed effects can be transferred to the corresponding patients.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IL: interleukin; 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 adults with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor).

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

Table 4: Research questions of the benefit assessment of guselkumab

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

a. Presented 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. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
c. Continuation of an inadequate therapy does not concur with the specified ACT.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

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

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

In its dossier, the company refers to consultations held on 20 July 2017 [3] und 22 December 2021 [4] and follows the ACT specified by the G-BA on 8 June 2022. On 27 May 2025, shortly before the dossier was submitted by the company, the G-BA had updated the ACT. In this assessment, the added benefit was assessed in comparison with the updated ACT of the G-BA presented in Table 4.

For both research questions, the company identified adalimumab, infliximab, ustekinumab or vedolizumab as an ACT. In doing so, the company deviates from the G-BA’s updated specification, as it does not consider risankizumab for question 1 and risankizumab and upadacitinib for question 2. 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 risankizumab and upadacitinib (see Chapter I 3).

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on 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 Studies included

The studies listed in the following Table 5 were 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])
GALAXI 1	Yes	Yes	No	Yes [5]	Yes [6-8]	Yes [9]
GALAXI 2	Yes	Yes	No	Yes [10]	Yes [6-8]	No
GALAXI 3	Yes	Yes	No	Yes [11]	Yes [6-8]	No

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.
RCT: randomized controlled trial

The studies GALAXI 1, GALAXI 2 and GALAXI 3, which compare guselkumab with ustekinumab, were used for the benefit assessment. The study pool was consistent with that selected by the company.

I 3.2 Study characteristics

As the included studies GALAXI 1, GALAXI 2 and GALAXI 3 are relevant to both research questions of this benefit assessment, the characteristics common to both research questions are described below. Research question-specific characteristics for research question 1 are described in Section I 4.1, and those for research question 2 are described in Section I 5.1.

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GALAXI 1	RCT, double-blind, parallel	Adult patients with moderately to severely active Crohn's disease[b, c] with ▪ SES-CD total score[d] ▫ ≥ 6 in cases of colonic or ileocolonic disease, or ▫ ≥ 4 for isolated ileal disease as well as ▪ confirmed inadequate response or intolerance to ≥ 1 ▫ conventional therapies (corticosteroids[e] or immunosuppressants[f]) or ▫ biologic therapy (TNFα antagonists or integrin inhibitors[g])	Guselkumab 1200 mg IV every 4 weeks → 200 mg SC every 4 weeks (N = 73)[h] guselkumab 600 mg IV every 4 weeks → 200 mg SC every 4 weeks (N = 73)[h] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 73) ustekinumab (N = 71) Placebo (N = 70)[h] relevant subpopulation thereof[i]: ▪ subpopulation A[j] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 35) ustekinumab (n = 30) ▪ subpopulation B[k] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 38) ustekinumab (n = 41)	Screening: up to 5 weeks treatment: 48 weeks[l] observation: up to 16 weeks[i] after the last dose of the study treatment	128 centres in Australia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Canada, Czech Republic, Croatia, France, Germany, Georgia, Greece, Israel, Italy, Japan, Jordan, Latvia, Lebanon, Lithuania, Macedonia, Malaysia, New Zealand, Poland, Republic of Korea, Russia, Serbia, Slovakia, Spain, Taiwan, Turkey, Ukraine, United States 05/2018–06/2024 data cut-offs: interim analyses[m] 20 August 2020[n]	Primary: Change in CDAI (Week 12) secondary: morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GALAXI 2	RCT, double-blind, parallel	see GALAXI 1	guselkumab 200 mg IV every 4 weeks → 200 mg SC every 4 weeks (N = 148)[h] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 148) ustekinumab (N = 150) placebo (N = 77)[h] relevant subpopulations thereof: ▪ subpopulation A[j] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 70) ustekinumab (n = 68) ▪ subpopulation Bk guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 79) ustekinumab (n = 82)	see GALAXI 1	186 centres in Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada; Czech Republic, China, France, Georgia, Germany, India, Israel, Italy, Japan, Jordan, Latvia, Lebanon, Macedonia, Malaysia, the Netherlands, New Zealand, Poland, Portugal, Republic of Korea, Russia, Saudi Arabia, Serbia, Slovakia, Spain, Taiwan, Tunisia, Turkey, Ukraine, Hungary, United States 01/2020–ongoing data cut-off: 20 October 2023[n]	Coprimary: ▪ CDAI response (Week 12) and CDAI remission (Week 48); ▪ CDAI response (Week 12) and endoscopic response (Week 48) secondary: morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GALAXI 3	RCT, double-blind, parallel	see GALAXI 1	guselkumab 200 mg IV every 4 weeks → 200 mg SC every 4 weeks (N = 151)[h] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 148) ustekinumab (N = 150) placebo (N = 76)[h] relevant subpopulations thereof: ▪ subpopulation A[j] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 70) ustekinumab (n = 72) ▪ subpopulation B[k] guselkumab 200 mg IV every 4 weeks → 100 mg SC every 8 weeks (N = 78) ustekinumab (n = 78)	see GALAXI 1	198 centres in Australia, Belarus, Belgium, Bosnia and Herzegovina, Brazil, Canada, China, Colombia, Croatia, Czech Republic, France, Georgia, Germany, Hungary, India, Israel, Italy, Japan, Jordan, Latvia, Lebanon, Macedonia, Malaysia, the Netherlands, New Zealand, Poland, Portugal, Republic of Korea, Russia, Saudi Arabia, Serbia, Slovakia, Spain, Taiwan, Tunisia, Turkey, Ukraine, United Kingdom, United States 01/2020–ongoing data cut-off: 16 October 2023[n]	see GALAXI 2

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

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

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Clinically active Crohn's disease, defined as a CDAI score of ≥ 220 to ≤ 450 and one of the following criteria: daily average stool frequency > 3 (number of liquid or very soft stools) or daily average abdominal pain > 1 according to the abdominal pain component of the CDAI (scale ranging from 0 = none to 3 = strong pain) at the start of the study.
c. Crohn's disease or Crohn's disease with fistula formation (duration ≥ 3 months) involving radiologically, histologically and/or endoscopically confirmed colitis, ileitis or ileocolitis.
d. Based on the presence of ulceration in ≥ 1 of 5 ileocolonic segments, resulting in the following specific scores for the ulceration components: ≥ 1 for the components ulceration size and ulcerated surface area; centrally recorded ≤ 21 days to > 8 days prior to randomization. The inclusion criterion was adjusted with Protocol Amendment 3 (20 October 2020). Prior to this date, patients with a Simple Endoscopic Score for Crohn's Disease (SES-CD) total score of ≥ 3 were included. The study documents show that, as a result, in each study a maximum of 10% of the patients included had a SES-CD total score of < 4 (in cases of isolated ileal disease) or < 7 (in cases of colonic or ileocolonic disease).
e. Including budesonide and beclometasone dipropionate
Criteria for corticosteroid failure:
- A non-response to corticosteroids is defined as an inadequate response, recurrent disease or a relapse despite 2-week treatment with oral or intravenous prednisone (or equivalent) at a dose of ≥ 0.75 mg/kg/day or ≥ 40 mg/day; or ≥ 4-week treatment with budesonide ≥ 9 mg/day or beclometasone dipropionate ≥ 5 mg/day;
- Intolerance is defined as the occurrence of clinically significant AEs (e.g. osteonecrosis/osteoporosis, psychosis, uncontrolled diabetes mellitus), which do not subside under a reduced dosage and which, in the investigator's opinion, preclude the continued use of corticosteroids, or the presence of a contraindication.
- Corticosteroid dependence is defined as the inability to taper off corticosteroids within 3 months of starting treatment without the recurrence of signs and/or symptoms of active Crohn's disease, or a relapse within 3 months after corticosteroid discontinuation

f. AZA, 6-MP or MTX
Criteria for immunosuppressant failure:
- Non-response is defined as an inadequate response, recurrent disease or relapse despite treatment with one of the following drugs for ≥ 3 months: 6-MP (1 mg/kg/day), AZA (2 mg/kg/day) or MTX (25 mg/week; IM or SC) or the highest tolerated dose in cases of leukopenia/elevated liver enzymes/nausea, or the confirmed therapeutically effective dose determined by blood test. If a lower dose was administered in accordance with local guidelines, this had to be documented.
- An intolerance is defined as the occurrence of clinically significant adverse events (e.g. pancreatitis, arthritis accompanied by high fever and/or a rash, leukopenia or persistently elevated liver enzymes), which do not subside following a dose reduction and which, in the investigator's opinion, preclude further use, or the presence of a contraindication.

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

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

g. Criteria for the failure of biologic agents:

- initially inadequate response to treatment: persistent symptoms and signs despite induction therapy with infliximab, adalimumab, certolizumab pegol or vedolizumab (≥ 2 weeks after the last dose) at a dosage approved for induction (as per SmPC) or
- loss of response to treatment: initial response to induction therapy followed by persistent symptoms and signs despite ≥ 2 doses of maintenance therapy with infliximab, adalimumab, certolizumab pegol or vedolizumab (≥ 2 weeks after the last dose) at a dosage approved for maintenance therapy (as per SmPC) or
- intolerance: reactions that meet one of the following three criteria: 1) a significant acute infusion/administration reaction; 2) a significant delayed infusion/administration reaction (e.g. (serum sickness-like reactions) or 3) significant injection site reactions following ≥ 1 dose of infliximab, adalimumab, certolizumab pegol or vedolizumab, which, in the investigator’s opinion, precluded continuation of treatment and occurred ≤ 24 hours after administration.

h. The arm is irrelevant for the assessment and is no longer presented in the following tables.

i. Following the interim analysis at Week 12, an urgent safety measure was implemented due to a case of toxic hepatitis in the guselkumab 1200 mg (IV) arm, resulting in the suspension of the induction phase in all arms. At that point, 51 of the 360 patients randomized in total had not yet completed their induction therapy; their treatment was discontinued. The treatment affected 10 patients in each of subgroups A and B (n = 6 in the study arm guselkumab 200 mg (IV) every 4 weeks → 100 mg (SC) every 8 weeks arm and n = 4 in the study arm ustekinumab).

j. Adult 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.

k. Adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to treatment with biologics.

l. Following the survey at the end of the 48-week blinded treatment phase, patients whom the investigator deemed would benefit from continued treatment with the study medication were eligible to enter a long-term extension study, under which they could continue to receive the respective study medication for up to 196 weeks. For patients who did not participate in the long-term extension study or who discontinued the study, the final study visit took place up to 16 weeks after discontinuation of treatment.

m. Two interim analyses had been prespecified:

- Interim analysis 1: after 250 patients had completed the survey at Week 12 or discontinued the study before Week 12 (initial dose-determination cohort).
- Interim analysis 2: after the initial dose-determination cohort had completed the survey at Week 24 or discontinued the study before Week 24.

n. Prespecified analysis at Week 48.

6-MP: 6-mercaptopurine; AE: adverse event; AZA: azathioprine; CDAI: Crohn’s Disease Activity Index; IV: intravenous; MTX: methotrexate; n: relevant subpopulation; N: number of randomized patients; ND: no data; Q4W: every 4 weeks; Q8W: every 8 weeks; RCT: randomized controlled trial; SC: subcutaneous; SES-CD: Simple Endoscopic Score for Crohn’s Disease; TNF: tumour necrosis factor

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

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td rowspan="3">GALAXI 1/GALAXI 2/GALAXI 3</td><td>Guselkumab
▪ weeks 0, 4, 8: 200 mg, IV
▪ weeks 16, 24, 32, 40: 100 mg, SC</td><td>Ustekinumab
▪ week 0: 6 mg/kg, IV
▪ weeks 8, 16, 24, 32, 40: 90 mg, SC</td></tr>
<tr><td colspan="2">Dose adjustments: not allowed</td></tr>
<tr><td colspan="2">Required pretreatment
▪ ≥ 1 of the following therapies (with the restrictions specified below)
▫ conventional therapies (corticosteroids or immunosuppressants[f])
or
▫ biologic therapies (TNFα antagonists or integrin inhibitors)
disallowed prior and concomitant treatment
▪ bowel resection ≤ 6 months or an intra-abdominal or other major surgery ≤ 12 weeks before the start of the study
▪ presence of a stoma
▪ corticosteroids (IV) ≤ 3 weeks before the start of the study
▪ cyclosporin, tacrolimus, sirolimus or mycophenolate mofetil ≤ 8 weeks before the start of the study
▪ 6-thioguanine ≤ 4 weeks before the start of the study
▪ initiation of biologic therapies:
▫ TNF-α antagonists ≤ 8 weeks before the start of the study[a]
▫ vedolizumab ≤ 12 weeks before the start of the study[a]
▫ ustekinumab ≤ 16 weeks before the start of the study[a]
▫ other immunomodulatory biologics[b]
▪ non-autologous stem cell therapy, natalizumab, efalizumab, B- or T-cell-depleting biologics (e.g. rituximab, alemtuzumab or visilizumab) ≤ 12 months before the start of the study
▪ apheresis or total parenteral nutrition for Crohn’s disease ≤ 3 weeks before the start of the study
▪ anti-IL-12/23p40 or anti-IL-23p19 antibodies (e.g. briakinumab, brazikumab, guselkumab, mirikizumab and risankizumab)[c]
allowed concomitant treatment[d]
▪ oral 5-ASA preparations[e]
▪ oral corticosteroids (prednisone ≤ 40 mg/day or equivalent, budesonide 9 mg/day or beclometasone dipropionate 5 mg/day)[f]
▪ conventional immunosuppressants (i.e. AZA, 6-MP, MTX)[g]
▪ antibiotics specific to Crohn's disease[h]
▪ enteral nutrition specific to Crohn's disease[i]</td></tr>
</table>

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

Study	Intervention	Comparison
a. A shorter wash-out period is acceptable if the drug concentration is below the limit of detection. b. ≤ 12 weeks or ≤ 5 half-lives before the start of the study, whichever is longer. c. Patients who had been treated with ustekinumab in accordance with the SmPC prior to the start of the study, who met the washout criteria defined in the study protocol, and who did not show any treatment failure or intolerance to ustekinumab were not excluded from participation in the study. d. Discontinuation or dose reduction after week 0 only at the investigator’s discretion. e. Unchanged at a dose that has been stable for ≥ 2 weeks prior to the start of the study or discontinued for ≥ 2 weeks; Weeks 0 to 48: no initiation of treatment with oral or rectal 5-ASA preparations. f. Unchanged up to Week 12 at a dose that had been stable for ≥ 2 weeks prior to the start of the study; from Week 12 onwards, all patients on corticosteroid therapy (unless this was not possible for medical reasons), tapering in accordance with the following schedule: For initial dose > 15 mg/day prednisone or equivalent, taper daily dose by 5 mg/week until 10 mg/day, then continue tapering by 2.5 mg/week until 0 g/day; for initial dose 11 to 15 mg/day prednisone or equivalent, taper daily dose to 10 mg/day over a 1-week period, then taper by 2.5 mg/week until 0 mg/day; ≤ 10 mg/day prednisone or equivalent, taper daily dose by 2.5 mg/week until 0 mg/day; for patients receiving budesonide, taper daily dose by 3 mg every 3 weeks to 0 mg/day. If clinical symptoms recur during the taper, tapering can be interrupted and/or the dose can be temporarily re-creased. In these cases, tapering should be continued within 4 weeks. g. For ≥ 12 weeks; unchanged at a dose that had been stable for ≥ 4 weeks before the start of the study or that had been discontinued ≥ 4 weeks; Weeks 0 to 48: no initiation of treatment. h. Unchanged at a dose that had been stable for ≥ 3 weeks prior to the start of the study or discontinued for ≥ 3 weeks; Weeks 0 to 48: no initiation of treatment. i. Administered for ≥ 2 weeks prior to the start of the study or discontinued for ≥ 2 weeks; Weeks 0 to 48: no initiation of treatment.		
5-ASA: 5-aminosalicylic acid; 6-MP: 6-mercaptopurine; AZA: azathioprine; IL-23p19: interleukin-23, p19 subunit; IL-12/23p40: Interleukin-12/23, p40 subunit; IV: intravenous; MTX: methotrexate; RCT: randomized controlled trial; SC: subcutaneous; TNF: tumour necrosis factor		

The studies presented by the company form part of an ongoing global phase 2/3 study programme. The GALAXI 1 study is a dose-ranging study, whilst the studies GALAXI 2 and GALAXI 3 are phase 3 studies with an identical design, conducted in parallel. Differences between the studies are listed below in the joint study description. Following each survey at the end of the 48-week blinded treatment phase, patients whom the investigator deemed would benefit from continued treatment with the assigned study medication were eligible to enter a long-term extension study and continue to receive the respective study medication for up to 4 years.

The studies GALAXI 1, GALAXI 2 and GALAXI 3 are double-blind, multicentre RCTs comparing guselkumab at various doses with ustekinumab and placebo in adults with moderately to severely active Crohn’s disease. The inclusion criteria were identical across the three studies.

The initial diagnosis of Crohn’s disease must have been established at least 3 months before enrolment.

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

- Crohn's Disease Activity Index (CDAI) score ≥ 220 to ≤ 450 and
- an average daily stool frequency (SF) > 3 with liquid or very soft stools (recorded using the CDAI-SF) or an average daily abdominal pain score (AP) > 1 (recorded using the CDAI scale for abdominal pain [CDAI-AP]; scale range of 0 = none, 1 = mild, 2 = moderate, 3 = severe pain) and
- Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥ 6 for colonic or ileal-colonic disease, or SES-CD of ≥ 4 for isolated ileal disease.

For this benefit assessment, it is assumed on the basis of the inclusion criteria that patients in the GALAXI studies had moderately to severely active Crohn's disease.

To be eligible for study participation, patients had to have received at least one conventional therapy (i.e. corticosteroids, immunosuppressants) or at least one treatment with biologics (e.g. TNFα antagonist or integrin inhibitor).

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

- inadequate response with or intolerance to
  - Corticosteroids (including prednisone, budesonide and beclomethasone dipropionate) or
  - Immunosuppressants AZA, 6-MP or MTX.
- corticosteroid-dependent disease (i.e. corticosteroids cannot be discontinued without the symptoms of Crohn's disease returning)

Patients may already have received biologic therapy (i.e. a TNF antagonist or vedolizumab) without, however, having shown any intolerance or an inadequate response.

Non-eligibility for treatment with biologics was defined as primary non-response (i.e. no initial response) or secondary non-response (i.e. loss of response whilst on continuous treatment) or intolerance to at least one biologic therapy (i.e. adalimumab, infliximab, certolizumab pegol, vedolizumab).

Patients who had received pretreatment with an IL-12/23 or IL-23 drug were excluded from the study. An exception was made for patients who had received a minimum amount of ustekinumab at the approved dose and who had both met the required washout criterion and shown no failure of or intolerance to ustekinumab.

Patients who had been treated with stable doses of corticosteroids for at least 2 weeks prior to the start of the study were eligible to participate in the study (see Table 7 for details on dosing and the tapering regimen for corticosteroids after randomization).

The studies GALAXI 1, GALAXI 2 and GALAXI 3 were conducted under a joint registration entry and study protocol. In all three studies, randomization was stratified by CDAI score (≤ 300 vs. > 300) and non-eligibility for a biologic agent (yes vs. no). In the studies GALAXI 2 and GALAXI 3, randomization was additionally stratified by SES-CD (≤ 12 vs. > 12) and corticosteroid therapy at the start of the study (yes vs. no). The stratification factor non-eligibility for a biologic agent subdivides the study populations into the subpopulations relevant for research question 1 (no: patients who are not eligible for conventional therapy) and research question 2 (yes: patients who are not eligible for a biologic agent) of this dossier assessment. The 5-arm study GALAXI 1 investigated 3 different dosing regimens of guselkumab. The four-arm studies GALAXI 2 and GALAXI 3 investigated two different dosing regimens for guselkumab. For the present benefit assessment, the relevant intervention is guselkumab administered at an induction dose of 200 mg as an IV infusion in Weeks 0, 4 and 8, and a subsequent maintenance dose of 100 mg as a SC injection in Weeks 16, 24, 32 and 40, compared with ustekinumab.

In the GALAXI 1 study, a total of 360 patients were randomly allocated in a 1:1:1:1:1 ratio to treatment with guselkumab (each study arm N = 73), ustekinumab (N = 71) or placebo (N = 70). The sub-populations relevant to research questions 1 and 2, comprising patients unsuitable for conventional therapy and patients unsuitable for biologic therapy respectively, comprise 35 and 38 patients from the guselkumab arm relevant to this benefit assessment, and 30 and 41 patients from the ustekinumab arm.

In the studies GALAXI 2 and GALAXI 3, a total of 523 and 525 patients were randomized in a 2:2:2:1 ratio to treatment with guselkumab, ustekinumab (N = 150 each) or placebo (N = 77 and N = 76). In the GALAXI 2 study, the sub-populations of patients who were no candidates for conventional therapy or biologics comprised 70 and 79 patients, respectively, in the guselkumab arm relevant to this benefit assessment, and 68 and 82 patients, respectively, in the ustekinumab arm. In the GALAXI 3 study, the subpopulations of patients who were non-responders to conventional therapy and biologics comprised 70 and 78 patients, respectively, in the guselkumab arm relevant to this benefit assessment, and 72 and 78 patients, respectively, in the ustekinumab arm.

Corticosteroid therapy (prednisone ≤ 40 mg/day or equivalent), which had been administered at a stable dose for at least 2 weeks prior to the start of the study, should be continued at this dose until Week 12. From Week 12 onwards, all patients receiving corticosteroid therapy were required to taper off the dose according to a set schedule (see Table 7 for details), unless this was not possible for medical reasons. If clinical symptoms recurred during dose reduction, the reduction could be interrupted, and a temporary increase in dose was also possible. In these

cases, tapering was to be continued within 4 weeks. Treatment with corticosteroids should not be started before Week 48 at the earliest. If it was necessary to start treatment for medical reasons, this was not regarded as a deviation from the protocol.

Treatment duration in the studies GALAXI 1, GALAXI 2 and GALAXI 3 was 48 weeks, or until treatment with a medication not permitted in the study or other therapy was initiated, or until unacceptable toxicity occurred, or until treatment was discontinued at the investigator’s decision or at the patient’s request.

The primary outcome in the GALAXI 1 study was the change in CDAI at Week 12. In the studies GALAXI 2 and GALAXI 3, the two co-primary outcomes were:

- CDAI response (defined as a reduction of ≥ 100 points compared with baseline or a CDAI score < 150) at Week 12 and CDAI remission (defined as a CDAI score < 150) at Week 48
- CDAI response at Week 12 and endoscopic response at Week 48

Patient-relevant outcomes of morbidity, health-related quality of life and side effects were additionally recorded.

Limitations of the GALAXI studies

The results of the studies GALAXI 1, GALAXI 2 and GALAXI 3 will be used for the benefit assessment. However, there were limitations, which are described below.

Lack of options for escalating the intervention

The company presented data only for the standard treatment regimen. In the GALAXI studies, the intervention was induced with an IV administration of 200 mg guselkumab in Weeks 0, 4 and 8. In addition to the dosing regimen chosen by the company, the SmPC recommends a further dosing regimen of 400 mg administered as a subcutaneous injection in Weeks 0, 4 and 8 [12-14]. From Week 16 onwards, patients in the GALAXI studies received 100 mg of guselkumab subcutaneously every 8 weeks as maintenance therapy, with no option to escalate treatment. According to the SmPC, the recommended maintenance dose following completion of the induction phase is 100 mg, administered as a subcutaneous injection every 8 weeks from Week 16 onwards. A notably higher maintenance dose of 200 mg administered as a subcutaneous injection from Week 12 onwards and every 4 weeks thereafter may be considered for patients who, in the physician’s opinion, do not show sufficient therapeutic benefit following the induction treatment [12-14]. In the GALAXI studies, patients in the relevant intervention arm may therefore have received an insufficient dose of guselkumab. It is unclear to what extent this deviation from the SmPC influenced the effects of the patient-relevant outcomes observed in the studies. This uncertainty was taken into account when assessing the certainty of conclusions (see Section I 4.2.2).

Comparator therapy not administered in full compliance with the SmPC

In the GALAXI studies, the comparator therapy with ustekinumab was induced with a weight-based intravenous induction dose in accordance with the SmPC [15]. In Week 8 following induction, maintenance therapy began with the first subcutaneous administration of ustekinumab. Thereafter, patients received ustekinumab SC every 8 weeks. According to the SmPC, the first subcutaneous dose of ustekinumab was to be administered 8 weeks after the intravenous dose, and subsequent doses are recommended every 12 weeks [16,17]. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Based on the clinical assessment, these patients may then receive the next dose either every 8 weeks or every 12 weeks. In the GALAXI studies, patients in the relevant comparator arm therefore may have been overdosed with ustekinumab. It is unclear to what extent this deviation from the SmPC influenced the effects of the patient-relevant outcomes observed in the studies. This uncertainty was taken into account when assessing the certainty of conclusions (see Section I 4.2.2).

Lack of independence of the studies GALAXI 2 and GALAXI 3

The studies GALAXI 2 and GALAXI 3 have identical study designs and investigate the same primary and secondary outcomes with the same statistical analysis plan. They are powered separately for the primary outcomes. The joint analysis (i.e. pooling) of GALAXI 2 and GALAXI 3 was prespecified. In the study protocol, the company states that the reason for conducting two confirmatory studies is to obtain independent confirmation of clinical efficacy in two independent patient samples, as required by some health authorities. However, the studies GALAXI 2 and GALAXI 3 were conducted simultaneously at largely the same study centres. This means that patients were divided between two trials at the same centres, under the supervision of the same investigators. In Module 4 A/B, the company states that the study populations for the studies GALAXI 2 and GALAXI 3 constitute a single sample. This view is shared. The studies GALAXI 2 and GALAXI 3 are therefore no independent studies. The company primarily presents meta-analyses that take into account the respective results of the GALAXI 1 study and those of an analysis of pooled data from the studies GALAXI 2 and GALAXI 3. Hereinafter, the term GALAXI 2/3 is used to refer to the pooled data from the studies GALAXI 2 and GALAXI 3. The certainty of conclusions of the results from the pooled GALAXI 2/3 data initially corresponds to that of the results from one study (see Section I 4.2.2).

Discontinuation of prior therapy with a biologic agent without treatment failure

The subpopulations from GALAXI 1 and GALAXI 2/3 relevant to research question 1 also included patients who had received prior treatment with a biologic without experiencing treatment failure. It was unclear why treatment with the respective biologic agent was discontinued in these patients and whether there was a therapeutic indication for switching treatment. Since the proportion of patients affected was similarly small across all studies in both arms (see Table 8), this was of no consequence for this benefit assessment.

Primary analysis population in the GALAXI 1 study

In the GALAXI 1 study, an urgent safety measure was implemented following a case of toxic hepatitis in the treatment arm in which an induction dose of 1200 mg of guselkumab was administered intravenously. All 51 (14%) of the 360 randomized patients who had not yet completed their induction treatment at that point had to discontinue their respective study treatment. Across all research questions, this applies to 16% of the guselkumab arm relevant for the benefit assessment and 11% of the ustekinumab arm. Excluding all patients who had been enrolled in the study less than 8 weeks ago does not result in any bias, but merely in a reduced precision. Consequently, the analyses presented by the company based on the primary analysis population are used for the outcomes relating to morbidity and health-related quality of life. For the outcome all-cause mortality and the outcomes of the side effects category, the analyses submitted by the company based on the randomized patients will be used. As the difference between the two populations is sufficiently small, considering the different analysis populations has no consequences in this situation.

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

I 4.1 Study characteristics (specific to research question 1)

For characteristics of the studies that apply to all research questions, see Section I 3.2.

I 4.1.1 Patient characteristics

Table 8 shows the characteristics of the patients in the subpopulation relevant to research question 1 in the studies included.

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

Study characteristic category	**GALAXI 1**		**GALAXI 2/3**	
	guselkumab	**ustekinumab**	**guselkumab**	**ustekinumab**
	N[a] = 29	**N[a] = 26**	**N[b] = 140**	**N[b] = 140**
Age [years]				
Mean (SD)	40 (15)	36 (11)	37 (13)	36 (13)
Median [Q1; Q3]	38 [28; 53]	36 [27; 42]	33.5 [27; 43][c]	34 [26; 43.5][d]
Sex [F/M], %	34/66	27/73	48/52	44/56
Region, n (%)				
Asia	4 (14)	1 (4)	20 (14)	12 (9)
Eastern Europe	22 (76)	25 (96)	99 (71)	101 (72)
North America	1 (3)	0 (0)	11 (8)	8 (6)
Rest of the world	2 (7)	0 (0)	10 (7)	19 (14)
Time since diagnosis of Crohn's disease [months]				
Median [Q1; Q3]	4.2 [1.9; 9.8]	4.5 [2.0; 10.6]	3.3 [0.9; 8.1]	3.0 [1.0; 7.6]
Disease location[e], n (%)				
Ileum isolated	7 (24)	3 (12)	33 (24)	29 (21)
Colon isolated	15 (52)	14 (54)	61 (44)	53 (38)
Ileocolon	7 (24)	9 (35)	46 (33)	58 (41)
Fistulae, n (%)	7 (24)	7 (27)	31 (22)	33 (24)
≥ 1 open or draining fistula	2 (7[f])	5 (19[f])	21 (15[f])	12 (9[f])
SES-CD total score, mean (SD)	12.0 (6.8)	13.4 (8.3)	11.9 (7.0)	12.1 (7.3)
CDAI total score, mean (SD)	301.4 (52.5)	315.1 (60.0)	298.2 (55.1)	290.2 (51.8)

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

Study characteristic category	**GALAXI 1**		**GALAXI 2/3**	
	guselkumab	**ustekinumab**	**guselkumab**	**ustekinumab**
	N[a] = 29	**N[a] = 26**	**N[b] = 140**	**N[b] = 140**
PRO2 components, n (%)				
Stool frequency (CDAI-SF)				
Per day mean (SD)	4.6 (2.6)	5.5 (2.3)	4.7 (2.3)	4.8 (2.5)
> 3 per day, n (%)	20 (69)	23 (88)	107 (76)	105 (75)
Abdominal pain (CDAI-AP)				
Mean (SD)	2.2 (0.5)	2.1 (0.5)	2.1 (0.5)	2.0 (0.5)
> 1, n (%)	29 (100)	25 (96)	136 (97)	137 (98)
Stool frequency > 3 per day (CDAI-SF) and abdominal pain (CDAI-AP) > 1	20 (69)	22 (85)	103 (74)	102 (73)
IBDQ, mean (SD)				
IBDQ total score	124.6 (36.4)	129.3 (28.7)	127.4 (34.5)[g]	129.4 (29.3)[g]
IBDQ bowel symptoms	39.9 (11.0)	39.3 (9.7)	40.3 (9.7)[g]	40.6 (9.1)[g]
IBDQ systemic symptoms	17.0 (6.2)	17.0 (5.4)	17.5 (5.5)[g]	17.4 (5.6)[g]
PROMIS-29, mean (SD)				
Physical Component Summary (PHS)	ND	ND	43.8 (8.2)[g]	44.7 (7.6)[g]
Mental Health Summary score (MHS)	ND	ND	43.0 (8.3)[g]	42.8 (7.3)[g]
PROMIS Fatigue SF7a, mean (SD)	58.5 (9.3)	58.2 (7.1)	58.4 (8.3)	58.8 (7.9)
EQ-5D VAS, mean (SD)	48.0 (15.6)	54.7 (20.6)	52.5 (18.1)[g]	53.4 (17.4)[g]
PGIS, mean (SD)	3.4 (0.5)	3.4 (0.7)	3.4 (0.7)[g]	3.5 (0.6)[g]
Inadequate response, intolerance or dependence on corticosteroids, n (%)	21 (72)	14 (54)	115 (82)	110 (79)
Inadequate response	14 (48)	7 (27)	71 (51)	88 (63)
Intolerance	1 (3)	4 (15)	15 (11)	13 (9)
Dependence	13 (45)	7 (27)	60 (43)	44 (31)
Inadequate response or intolerance to immunosuppressants, n (%)	17 (59)	19 (73)	79 (56)	69 (49)
Inadequate response	14 (48)	17 (65)	70 (50)	59 (42)
Intolerance	9 (31)	3 (12)	22 (16)	20 (14)
Prior therapy with a biologic agent without treatment failure, n (%)	4 (14)	7 (27)	17 (12)	15 (11)
Treatment discontinuation, n (%)	4 (14)[h]	2 (8)[h]	14 (10)[i, j]	15 (11)[i, j]
Study discontinuation, n (%)	2 (7)[k]	0 (0)[k]	9 (6)[l, m]	9 (6)[l, m]

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

Study characteristic category	GALAXI 1		GALAXI 2/3	
	guselkumab	ustekinumab	guselkumab	ustekinumab
	N[a] = 29	N[a] = 26	N[b] = 140	N[b] = 140

a. Number of randomized patients in subpopulation A whose treatment was not discontinued during the induction phase as a result of the safety measure (primary analysis population; see Section I 3.2). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Median [Q1; Q3] in GALAXI 2: 35 [28; 51]; in GALAXI 3: 33 [26; 42].
d. Median [Q1; Q3] in GALAXI 2: 34 [26; 42]; in GALAXI 3: 34 [26; 45].
e. Based on a central assessment.
f. Institute's calculation.
g. Module 4 A contains varying information regarding the baseline values. The values in the table correspond to Module 4 A, Section 4.3.1.3, and are based on the patients for whom values were available at the start of the study. In GALAXI 2/3, there were 138 vs. 138 patients each for IBDQ, PROMIS-29 and EQ-5D VAS, and 138 versus 139 patients for PGIS.
h. Reasons for treatment discontinuation in the intervention versus the control arm were the following (percentages based on the primary analysis population): in GALAXI 1: AEs (7% vs. 4%), worsening of the disease (3% vs. 0%), patient request (3% versus 4%).
i. Institute's calculation; in GALAXI 2, 3 (4%) patients in the intervention arm versus 8 (12%) patients in the comparator arm, and 11 (16%) versus 7 (10%) patients in the intervention arm of GALAXI 3 discontinued treatment.
j. Reasons for treatment discontinuation in the intervention arm versus the control arm (percentages based on randomized patients in subpopulation A) in GALAXI 2: patient request (1% vs. 6%), lack of efficacy (1% vs. 1%), worsening of the disease (0% vs. 3%), AEs (0% vs. 1%), lost to follow-up (1% vs. 0%); in GALAXI 3: AEs (7% vs. 1%), patient request (4% vs. 1%), pregnancy (0% vs. 3%), worsening of the disease (1% vs. 0%), Crohn's disease-related surgery (0% vs. 1%), other reasons (1% vs. 1%).
k. Reason for study discontinuation in the intervention vs. the control arm of GALAXI 1 was the following (percentages based on randomized patients): patient request (7% vs. 0%).
l. Institute's calculation; in GALAXI 2, 2 (3%) patients in the intervention arm versus 5 (7%) patients in the comparator arm, and in GALAXI 3, 7 (10%) patients in the intervention versus 4 (6%) patients in the comparator arm discontinued the study.
m. In GALAXI 2, reasons for study discontinuation in the intervention arm versus the control arm (percentages based on randomized patients in subpopulation A) were: patient request (1% vs. 7%), lost to follow-up (1% vs. 0%); in GALAXI 3: patient request (6% vs. 4%), lost to follow-up (1% vs. 1%), other reasons (3% vs. 0%).

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; F: female; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary score; n: number of patients in the category; N: number of analysed patients; ND: no data; PHS: Physical Health Summary score (Physical Component Summary); PRO2: patient-reported outcome 2; PROMIS: Patient-Reported Outcome Measurement Information System; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF-36: Short Form 36 Health Survey; VAS: visual analogue scale

The median age of the patients in the subgroup not eligible for conventional therapy ranged between 33.5 and 38 years. They had been diagnosed with Crohn's disease for a median of 3 to 4.5 years. The sex ratio was largely balanced in GALAXI 2/3; in GALAXI 1, the proportion of

men was higher. The majority of the patients came from the Eastern Europe. Overall, patients from Asia, North America and countries of the *Rest of the World* category, which includes Germany, accounted for a small proportion. The majority of patients had an average daily SF of > 3 (as measured by the CDAI-SF), and almost all of them reported abdominal pain of at least moderate intensity (> 1 measured with the CDAI-AP, scale range 0 = no pain to 3 = strong pain). In GALAXI 1 and GALAXI 2/3, prior treatment with corticosteroids had failed in 72% and 82% of patients in the guselkumab group, and in 54% and 79% of patients in the comparator group. In the studies GALAXI 1 and GALAXI 2/3, prior treatment with immunosuppressants had failed in 59% and 56% of patients, respectively, in the guselkumab group, and in 73% and 49% of patients, respectively, in the comparator group. A small proportion of patients had received prior therapy with a biologic agent without experiencing treatment failure. The proportion of patients who discontinued treatment or withdrew from the study was similarly high in both arms of the GALAXI 2/3 study (an average of 10% and 11% for treatment discontinuation, and 6% for study withdrawal). In GALAXI 1, more patients in the guselkumab group discontinued treatment prematurely than in the comparator group (14% vs. 8%), a trend that was also observed in study discontinuations (7% vs. 0%). Across all studies, the most common reasons for treatment discontinuation were AEs and patient request. The most common reason for dropping out across all studies was patient request.

Overall, the demographic and clinical characteristics of the patients included are considered to be sufficiently comparable.

I 4.1.2 Concomitant treatments

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

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

Study time point drug class drug	Patients with concomitant therapy n (%)	
	guselkumab	ustekinumab
GALAXI 1	N = 29	N = 26
Concomitant treatments at baseline	25 (86)	26 (100)
Oral corticosteroids	15 (52)	13 (50)
Oral corticosteroids (excluding budesonide/beclomethasone)	11 (38)	10 (38)
Budesonide	4 (14)	3 (12)
Beclomethasone	0 (0)	0 (0)
Immunosuppressants	6 (21)	15 (58)
Azathioprine or 6-mercaptopurine	6 (21)	15 (58)
Methotrexate	0 (0)	0 (0)
Concomitant treatments during the study	ND	ND
GALAXI 2/3	N = 140	N = 140
Concomitant treatments at baseline	118 (84)	111 (79)
Oral corticosteroids	65 (46)	63 (45)
Oral corticosteroids (excluding budesonide/beclomethasone)	38 (27)	36 (26)
Budesonide	29 (21)	27 (19)
Beclomethasone	0 (0)	0 (0)
Immunosuppressants	45 (32)	40 (29)
Azathioprine or 6-mercaptopurine	45 (32)	40 (29)
Methotrexate	0 (0)	0 (0)
Concomitant treatments during the study	ND	ND
n: number of patients with concomitant therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial		

At the start of the study, the majority of patients in the GALAXI studies were receiving concomitant therapy. The proportion of patients receiving corticosteroids was balanced between the two studies and the study arms. The proportion of patients receiving concomitant therapy with immunosuppressants at the start of the study was higher in the comparator group of the GALAXI 1 study (58%) than in the intervention arm (21%), and higher than in GALAXI 2/3 (32% vs. 29%). Information on concomitant therapies during the study is not available. However, the protocol included guidelines on concomitant treatment (see Table 7).

I 4.1.3 Risk of bias across outcomes (study level)

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

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

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
GALAXI 1	Yes	Yes	Yes	Yes	Yes	Yes	Low
GALAXI 2/3	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for each of the GALAXI studies.

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

The company states that at least 70% of the patients included in the study were white and that the study’s inclusion and exclusion criteria were also valid in the German health care context. The treatment algorithms set out in German, European and international guidelines showed a high degree of comparability. It can therefore be assumed that the health care standard for patients with Crohn’s disease is comparable. Overall, this ensures that the study participants adequately represent the target population within the German health care context and that the results are transferable. Furthermore, the subgroup analyses for the characteristic region did not suggest any relevant effect modification. The 8-week dosing interval for ustekinumab reflects the treatment reality for the vast majority of patients with ’s disease in Germany.

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

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

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

- Mortality
  - all-cause mortality

- Morbidity
  - corticosteroid-free remission, recorded using PRO2
  - bowel symptoms, recorded using the IBDQ subscore of bowel symptoms
  - systemic symptoms, recorded using the IBDQ subscore of systemic symptoms
  - absence of fistula
  - fatigue, recorded using the PROMIS Fatigue SF7a
  - symptoms, recorded using the PGIC and the PGIS
  - health status, recorded using the EQ-5D VAS
  - activity impairment, recorded using the WPAI-CD Item 6
- Health-related quality of life
  - recorded by IBDQ
  - recorded by PROMIS-29
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - infections, operationalized as infections and infestations (System Organ Class [SOC], AEs)
  - other specific AEs, if any

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

Table 11 shows the outcomes for which data were available in the studies included (yes/no).

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

Study	Outcomes												
	All-cause mortality[a]	Corticosteroid-free remission (PRO2)	Bowel symptoms, systemic symptoms (IBDQ)	Absence of fistula	Fatigue (PROMIS Fatigue SF7a)	Symptoms (PGIC, PGIS)	Health status (EQ-5D VAS)	Activity impairment (WPAI-CD Item 6)	Health-related quality of life (IBDQ, PROMIS-29)	SAEs	Discontinuation due to AEs	Infections[b]	Other specific AEs
GALAXI 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes[d]	Yes	Yes	Yes	No[e]
GALAXI 2/3	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	No[c]	Yes	Yes	Yes	Yes	No[e]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as infections and infestations (SOC, AEs).
c. No suitable data available; for the reasoning, see the following sections on the respective outcomes.
d. GALAXI 1 does not contain any suitable analyses for the PROMIS-29; for the reasons, see the following section on the PROMIS-29 sum score.
e. No further specific AEs were identified based on the AEs occurring in the relevant studies.

AE: adverse event; IBDQ: Inflammatory Bowel Disease Questionnaire; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO2: Patient-Reported Outcome 2; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; SAE: serious adverse event; SF7a: Short Form 7a; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn’s Disease

Outcomes on morbidity and health-related quality of life

Corticosteroid-free remission (PRO2)

In Module 4 A, the company presents several operationalizations on the remission:

- remission at Week 48
- sustained remission (remission in ≥ 80% of all surveys between Weeks 12 and 48 inclusive, corresponding to at least 8 out of 10 surveys, always including remission at Week 48)
- Intermittent corticosteroid-free remission at Week 48
- corticosteroid-free remission at Week 48, with at least 90 days of corticosteroid-free status prior to Week 48

Remission is recorded using PRO2. The PRO2 comprises the 2 scales of the CDAI on stool frequency (CDAI-SF) and on abdominal pain (CDAI-AP; on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe pain), each of which were recorded using a patient diary. According to the predefinition in the study design, remission by PRO2 was defined as a daily average SF (CDAI-SF) ≤ 3 and daily average abdominal pain (CDAI-AP) ≤ 1 (each averaged over a period of 7 days). In each case, neither value must be worse than it was at the start of the study. According to the information provided by the company in Module 4 A, the threshold values used are in line with the STRIDE-II recommendations for the preferred operationalization of remission [18]. The operationalization of remission based on these criteria corresponded to a largely symptom-free condition of the patients and was therefore face valid.

The operationalization of remission presented in Module 4 by means of PRO2 at Week 48 and the simultaneous absence of corticosteroid use for a period of at least 90 days prior to Week 48 (in short: corticosteroid-free remission (PRO2)), was deemed appropriate and adopted. This is justified below:

The current S3 guideline describes corticosteroid-free remission (i.e. without the use of systemic corticosteroids or oral budesonide) as an important treatment goal [19]. Achieving corticosteroid-free remission was considered patient relevant in this benefit assessment. According to current guidelines, systemic corticosteroids should generally not be used for remission maintenance due to serious side effects in long-term therapy, and their use should be minimized in clinical practice [19,20]. Achieving remission whilst remaining free of systemic corticosteroids is therefore a patient-relevant outcome from the perspective of avoiding long-term side effects. 90-day corticosteroid-free remission was also considered an operationalization for a more sustainable remission. For the operationalizations remission at Week 48, in contrast, sustained remission and intermittent corticosteroid-free remission, patients who achieve remission only while on corticosteroids—or who have received corticosteroids during at least the 90 days prior to Week 48—are also considered responders. Based on the dose reduction scheme used in the GALAXI studies to taper corticosteroids (see Section I 3.2), it was also assumed that corticosteroid-free remission was generally achievable for most patients. The high proportion of patients who achieved a corticosteroid-free remission at Week 48 (see Sections I 4.2.3 and I 5.2.3) also suggested that this was an achievable outcome in the therapeutic indication. The predefined 90-day period of a corticosteroid-free status as a prerequisite for corticosteroid-free remission is considered to be adequate in this context. If the disease relapses within 3 months of discontinuing corticosteroids, the disease is assumed to be corticosteroid-dependent according to current guidelines [19,20]. The results for the outcome remission (PRO2) are presented as supplementary information.

It should be noted that individual values for calculating the daily average might have been missing for patients with available data at Week 48. According to the statistical analysis plan of the GALAXI 1 study, any individual days (up to 2 of the 7 days) that were missing for the calculation of the mean were imputed by the mean of the known values. If fewer than 5 values were available, the mean was not calculated and reported as missing. It is unclear for how many patients values for individual days were missing. This led to additional uncertainty for this outcome, which went beyond the uncertainty described in the section on the risk of bias due to the high proportion of missing values (see Section I 4.2.2).

According to the study design, remission was predefined using the CDAI. However, in addition to the patient-relevant components included in PRO2 (SF and abdominal pain), the CDAI also incorporates parameters that do not represent changes immediately perceptible to patients (e.g. examinations: haematocrit, body weight). The definition of remission using the CDAI is therefore not suitable for the benefit assessment.

The company also presents further prespecified operationalizations on SF (recorded using the Bristol Stool Form Scale) and abdominal pain (recorded using the Abdominal Pain Numerical Rating Scale). These operationalizations are not used for assessment, as SF and abdominal pain are already adequately accounted for in the outcome corticosteroid-free remission. Irrespective of this, these analyses reveal no statistically significant difference between guselkumab and ustekinumab.

Health-related quality of life (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 exactly ≥ 15% of the scale range. As explained in the IQWiG *General Methods* [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 and exactly 15% of the scale range in analyses specified post-hoc. Since the patients included in the GALAXI studies were symptomatic (CDAI-SF > 3 or CDAI-AP > 1) at baseline and additional treatment with guselkumab could therefore in principle improve symptoms, the analyses of improvement are relevant for both the IBDQ and the PROMIS Fatigue SF7a and PROMIS-29. 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 available outcomes. 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.

Absence of fistula

The outcome absence of fistula is operationalized as the complete absence of open or draining fistulae, regardless of whether these were present at baseline or developed during the course of the study. The analyses on this operationalization specified post hoc for the benefit assessment are adequate.

In addition, analyses of the operationalizations of fistula response (a reduction by ≥ 50% in the number of open or draining fistulae at Week 48 compared with baseline in patients with at least one fistula at baseline) and complete fistula response (complete absence of open or draining fistulae at Week 48 in patients with at least one fistula at baseline) were prespecified in the studies GALAXI 1 and GALAXI 2/3.

The prespecified operationalizations of fistula response and complete fistula response are not suitable for the benefit assessment, as they only include patients who already had open or draining skin fistulae at the start of the study. Thus, the corresponding analyses did not consider patients in whom open or draining skin fistulae only occurred during the course of the study. As shown in Table 8 and Table 16, open or draining skin fistulae were present in only a small proportion (< 20 %) of patients at the start of the study. These analyses are therefore inadequate. Therefore, the adequate post-hoc operationalization absence of fistulae is used in the current data situation.

Outcomes relating to morbidity and health-related quality of life (PROMIS Fatigue SF7a and PROMIS-29) recorded using the PROMIS

The 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 GALAXI studies used the following patient-reported PROMIS questionnaires: PROMIS-29 v2.0 to record health-related quality of life, and PROMIS Fatigue SF7a to record fatigue. Moreover, analyses on fatigue based on the PROMIS Fatigue SF5a are available for GALAXI 2/3.

PROMIS Fatigue SF7a is used for the benefit assessment

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 [21,22].

According to the company, the PROMIS Fatigue SF5a is an individually compiled questionnaire comprising items 1–5 of the PROMIS Fatigue SF7a. Pursuant to the company, the PROMIS Fatigue SF5a was added in Amendment 1 to the Statistical Analysis Plan for the studies GALAXI 2 and GALAXI 3 in response to a query from the regulatory authorities as to whether changes in the PROMIS Fatigue SF7a were driven by specific items. The results should therefore be regarded as a supplement to the PROMIS Fatigue SF7a.

The PROMIS Fatigue SF 5a was prepared without patient involvement and without validation or psychometric testing in the target population. However, the PROMIS Fatigue SF7a is a comprehensively validated instrument, the validity of which in the present therapeutic indication was investigated among other things [23]. For this reason, the PROMIS Fatigue SF7a is used for the outcome fatigue in this benefit assessment.

For the PROMIS Fatigue SF7a, the company presented responder analyses for the following response criteria in Module 4 A and Module 4 B of its dossier:

- GALAXI 1: ≥ 8.07 points (post hoc)
- GALAXI 2/3: ≥ 9 points (predefined)

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 [21], resulting in a scale span of 53.8. Thus, the post-hoc response criterion of 8.07 points applied for the GALAXI 1 study corresponds exactly to 15% of the scale range. The response criterion of 9 points predefined in GALAXI 2/3 corresponds to 16.7% of the scale range. In the current data situation, the results from GALAXI 1 and GALAXI 2/3 for the PROMIS Fatigue SF7a are summarized in a meta-analysis based on the Institute's calculations.

Sum scores of the PROMIS-29 were used for the assessment

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 an 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 sum scores: Physical Health Summary Score (PHS) and Mental Health Summary Score (MHS). Both component summaries

incorporate all seven domains and the NRS, albeit with different weightings [24,25]. For both component summaries, a high value corresponds to a better health-related quality of life. The 2 sum scores were used for the benefit assessment. These were predefined in the statistical analysis plan for the studies GALAXI 2 and GALAXI 3 and provide a more comprehensive picture of health-related quality of life than a separate consideration of the individual domains. The results of the seven domain scores and the NRS for pain intensity are additionally presented.

The sum scores for the PROMIS-29 are standardized scores that do not have a fixed scale range. The procedure for determining the scale range in the specific situation of standardized values is described in detail in Appendix E of dossier assessment A21-86 dossier assessment on osimertinib [26]. Related to the PROMIS-29 v2.0, the PHS and MHS sum scores are calculated based on the coefficients specified in the PROMIS manual [24], which are derived from a sample of 3,000 individuals from the normal US population and were described by Hays et al. in 2018 [25]. As described in the PROMIS manual, some of the coefficients are negative. The inclusion of negative coefficients means that the minimum and maximum values of the PCS and MCS cannot be calculated by assigning the best or worst possible score to each item. The approach described in Module 4A and Module 4B for calculating the scale ranges of the PHS and MHS – which assigns the best or worst values to each of the seven domains and the NRS – is therefore not followed. Instead, analogous to the approach described in dossier assessment A21-86 [26], the scale range of the empirical minima and maxima from the sample by Hays et al. 2018 [25] is used for both sum scores of the PROMIS-29 v2.0 to determine the scale ranges and the response criteria derived therefrom of 15% of the respective range. This results in the following response criteria:

- PHS: score range 21.6 to 62.4 points; range 40.8 points; 15% = 6.12 points
- MHS: score range 19.5 to 62.3 points; span 42.8 points; 15% = 6.42 points

The company's dossier for the GALAXI 1 study does not contain any analyses of the PROMIS-29 in the form of the two sum scores, PHS and MHS, and thus no suitable data. For GALAXI 2/3, the company presents analyses of responder analyses on the improvement at Week 48, using the prespecified threshold values of ≥ 7 points and ≥ 9 points respectively, in Module 4 A and Module 4 B of its dossier. For PHS and MHS, this corresponds to the following proportions of the scale range, based on the empirical minima and maxima in the sample from Hays et al. 2018 [25]:

- PHS: 7 points = 17.2% of the scale range; 9 points = 22.1% of the scale range
- MHS: 7 points = 16.4% of the scale range; 9 points = 21.0% of the scale range

Furthermore, an improvement by ≥ 5 points was also a prespecified response criterion; however, this represents less than 15% of the scale range. As explained in the *General Methods* of the Institute [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (in post-hoc analyses exactly 15% of the scale range). The responder analyses submitted by the company, showing improvements of ≥ 7 points and ≥ 9 points, therefore meet these criteria. The predefined response criterion of an improvement by ≥ 7 points represents a sufficient approximation for a response criterion using 15% of the scale range and is used for the benefit assessment in the present data situation.

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

In accordance with the respective PROMIS manuals [21 PROMIS, 2025 #211], the raw values from the respective instrument must be converted into T-scores for analysis. Two types of scoring are described here. On the one hand, there is a so-called "Response Scoring Pattern", which can be calculated online via the HealthMeasures Scoring Service [27] 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. 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 GALAXI studies 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.

Symptoms (PGIC and PGIS)

The PGIC and PGIS scales each consist of a single question that the patients could use to assess the change in or the severity of the symptoms of Crohn's disease. Using PGIC, patients were asked to assess the change in disease severity on a 7-point scale (from 1 to 7: 'very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse', 'very much worse') in relation to the start of the study. Using the PGIS, patients should rate their current severity of disease on a five-point scale (from 1 to 5: 'none', 'mild', 'moderate', 'severe', 'very severe'). The respective specific question is set out in the study documents for the GALAXI studies and is face valid.

For PGIC, the company presented responder analyses based on the GALAXI 1 study in its dossier in which the scale values from 1 ('very much improved') to 3 ('mildly improved') were seen as an improvement. This analysis of any improvement is appropriate. For PGIS, the company presented responder analyses based on the GALAXI 1 study in its dossier in which the improvement by at least one point was seen as an improvement (corresponds to > 15% of the scale range [prespecified]). This analysis was also adequate [1]. Both PGIC and PGIS were recorded in all GALAXI studies. However, no responder analyses on an improvement by at least 1 point were predefined and conducted for the studies GALAXI 2 and GALAXI 3. Consequently, there are no analyses available for GALAXI 2/3 regarding this operationalization.

In Module 4, the company presents meta-analyses on the predefined response criterion of an improvement by at least 2 points for both the PGIC and the PGIS. However, this response threshold is clearly higher than the response threshold predefined for GALAXI 1, i.e. an improvement by at least 1 point. Mild but perceivable improvements are not taken into account in the analysis using the response threshold improvement by at least 2 points. In contrast, responder analyses based on the criterion improvement by at least 1 point take into account any improvement reported by the patient and thus provide an adequate and comprehensive picture of the improvement in symptoms. The responder analyses on an improvement by at least 1 point are therefore used for the benefit assessment.

Activity impairment (WPAI-CD Item 6)

The WPAI-CD is a questionnaire developed to measure the impairment of work productivity and of activities outside of work attributable to Crohn's disease [28]. Whilst the first five items relate to work productivity, item 6 assesses limitations on daily activities outside work due to Crohn's disease. This question measures the impairment of daily activities in the last 7 days on a scale from 0 to 10 and is face valid.

The study reports for the GALAXI studies contain analyses on WPAI-CD item 6, which include almost all patients in the respective study. The results for WPAI-CD item 6 therefore appear to be basically usable. However, the analyses available in the study reports relate to the total population of the respective study, whereas the questions addressed in the dossier assessment require analyses that relate to the respective relevant sub-population. However, the company does not present any WPAI-CD assessments in Module 4 A and Module 4 B of the dossier, nor does it explain the reasons. Therefore, no suitable data are available for the WPAI-CD item 6.

Mucosal healing

In the GALAXI studies, mucosal healing was recorded using imaging techniques (video ileocolonoscopy) and defined as the complete absence of ulcerations in all ileocolonic

segments of the intestine. However, this outcome is not patient-relevant per se, as there is not necessarily a connection to the directly noticeable 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 was therefore not used for the benefit assessment.

Hospitalizations, visits to emergency departments and surgeries related to Crohn’s disease

The company presented analyses on the following outcomes in Module 4 A and Module 4 B.

- Hospitalization for any reason (defined as admission to an emergency department, hospitalization or surgery for any reason; GALAXI 1 only)
- Admission to an emergency department, hospitalization or surgery due to Crohn’s disease (GALAXI 2/3 only)
- medical intervention due to Crohn's disease (GALAXI 1 only)
- Surgery for Crohn's disease (GALAXI 1 and GALAXI 2/3)
- Hospitalization due to Crohn's disease (GALAXI 2/3 only)

Hospitalization, admissions to the emergency department, surgeries and similar events resulting from Crohn’s disease can generally serve as suitable operationalizations for severe symptoms of Crohn’s disease.

However, Modules 4 A and 4 B do not specify which events are included in these outcomes. The electronic case report form (eCRF) indicates that this operationalization of the outcome may include interventions of significantly varying severity. On the one hand, this includes serious surgical procedures (such as bowel resection) that are associated with a severe course of the disease and potentially severe complications. On the other hand, this also includes less serious procedures (such as surgical fistula closure) carried out to treat acute symptoms. It is not appropriate to summarize such diverse events. The events listed in the eCRF could also be supplemented by other events which, in the investigator’s opinion, were related to Crohn’s disease. There was therefore no predefined list of events to be included in these analyses. Therefore, the presented analyses were not used for the benefit assessment.

The outcome hospitalization due to any cause is presented as supplementary information (see I Appendix B.1 of the full dossier assessment).

Outcome category of side effects

The company presented analyses on the outcomes AEs, SAEs and severe AEs, each with and without consideration of disease-related events. The company provides a list of Preferred

Terms (PTs) for defining disease-related events, which, in addition to the PT Crohn's disease, includes other non-specific PTs (e.g. (vomiting). The PTs fistulae, abscesses, stenoses/obstructions and intestinal perforations, however, are not considered disease-related events. On the one hand, this selection does not appear to be complete and, on the other, it remains unclear what rationale the company used when selecting the PTs. In the current data situation, the overall rates excluding disease-related events can nevertheless be used, as the differences between the overall rates with and without disease-related events can largely be explained by the PT Crohn's disease (see I Appendix C).

Operationalization of the outcome infections

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

I 4.2.2 Risk of bias

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

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

Study	Study level	Outcomes												
		All-cause mortality[a]	Corticosteroid-free remission (PRO2)	Bowel symptoms, systemic symptoms (IBDQ)	Absence of fistula	Fatigue (PROMIS Fatigue SF7a)	Symptoms (PGIC, PGIS)	Health status (EQ-5D VAS)	Activity impairment (WPAI-CD Item 6)	Health-related quality of life (IBDQ, PROMIS-29)	SAEs	Discontinuation due to AEs	Infections[b]	Other specific AEs
GALAXI 1	L	H[c]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	–[e]	H[d]	H[c]	L[f]	H[c]	–
GALAXI 2/3	L	H[c]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	–[e]	H[d]	H[c]	L[f]	H[c]	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as infections and infestations (SOC, AEs).
c. Incomplete observations for potentially informative reasons.
d. Due to the high proportion (≥ 10%) of values or the proportion of values that differs between the arms (> 5 percentage points) imputed using the NRI.
e. No suitable data available; for reasoning, see Section I 4.2.1 of this dossier assessment.
f. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs was assumed to be limited (see body of text below).

AE: adverse event; H: high; IBDQ: Inflammatory Bowel Disease Questionnaire; L: low; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PRO2: Patient-Reported Outcome 2; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; SAE: serious adverse event; SF7a: Short Form 7a; SOC: System Organ Class; VAS: visual analogue scale

In the GALAXI studies, the results for all outcomes, with the exception of discontinuation due to AEs, are subject to a high risk of bias.

For the results on the outcomes in the categories morbidity and health-related quality of life, this is due to the high proportion of values imputed using NRI, or the fact that this proportion varies between the arms.

In the subpopulation for research question 1, missing values were imputed in 11% of patients in GALAXI 1 and in 10% to 12% of patients in GALAXI 2/3, depending on the outcome. In the subpopulation for research question 2, the proportion of patients with imputed values was 17% in GALAXI 1 and, depending on the outcome, between 18% and 21% in GALAXI 2/3. The company's 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 imputed values.

With regard to the results for the outcome all-cause mortality and the outcomes in the AE category (excluding discontinuation due to adverse events), the reason for the high risk for bias is that, in each case, the data are incomplete for potentially informative reasons, as follow-up observation was discontinued after the end of treatment and is therefore potentially shortened. In the subgroup for research question 1, 14% vs. 8% discontinued treatment prematurely in GALAXI 1 and 10% vs. 11% in GALAXI 2/3; in the subgroup for research question 2, the figures were 16% vs. 16% and 15% vs. 20%, respectively.

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

Consideration of patients with corticosteroid therapy

According to the GALAXI study design, patients who initiated corticosteroid or immunosuppressant therapy during the study or who received corticosteroid therapy above their individual baseline level were considered non-responders for all efficacy outcomes. However, initiating corticosteroid therapy or increasing the dose of corticosteroids can be part of the treatment strategy in the given therapeutic indication, and also did not necessarily lead to discontinuation of the study medication in the GALAXI studies. Information on the corticosteroid dosage during the studies is not available. In total, treatment was discontinued in one patient of the GALAXI 3 study due to the administration of disallowed medication. In Module 4 A/B of its dossier, the company deviated from this prespecification and presented analyses including patients who initiated corticosteroid treatment or increased the corticosteroid dose from baseline, with the values actually recorded and thus without imputation. This approach was adequate.

Summary assessment of the certainty of conclusions

In addition to the biasing aspects described here, the uncertainties regarding the dosing of guselkumab and ustekinumab discussed in Section I 3.2, as well as the lack of independence of the GALAXI 2 and GALAXI 3 studies should be taken into account. Consequently, based on the GALAXI studies, at most hints, e.g. of an added benefit, can be derived on the basis of the GALAXI studies, both in case of a meta-analysis or when individual studies are considered.

I 4.2.3 Results

Table 13 summarizes the results of the comparison of guselkumab with ustekinumab in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix D.1 of the full dossier assessment.

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

Outcome category outcome study	Guselkumab		Ustekinumab		Guselkumab vs. ustekinumab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Mortality (until Week 48)					
All-cause mortality[b]					
GALAXI 1	35	0 (0)	30	0 (0)	–
GALAXI 2/3	140	0 (0)	140	0 (0)	–
Total					–
Morbidity (at Week 48)					
Corticosteroid-free remission (PRO2)[c]					
GALAXI 1	29	15 (51.7)	26	17 (65.4)	0.79 [0.50; 1.25]; 0.315
GALAXI 2/3	140	88 (62.9)	140	90 (64.3)	0.98 [0.82; 1.17]; 0.813
Total[d]					0.95 [0.80; 1.12]; 0.516
Remission (PRO2)[c] (supplementary presentation)					
GALAXI 1	*29*	*18 (62.1)*	*26*	*17 (65.4)*	*0.94 [0.64; 1.41]; 0.780*
GALAXI 2/3	*140*	*93 (66.4)*	*140*	*93 (66.4)*	*1.00 [0.85; 1.18]; 0.983*
Total[d]					*0.99 [0.85; 1.16]; 0.916*
Bowel symptoms (IBDQ – improvement)[e]					
GALAXI 1	29	22 (75.9)	26	19 (73.1)	1.04 [0.76; 1.42]; 0.806
GALAXI 2/3	140	95 (67.9)	140	96 (68.6)	0.99 [0.85; 1.16]; 0.928
Total[d]					1.00 [0.87; 1.15]; 0.978
Systemic symptoms (IBDQ – improvement)[f]					
GALAXI 1	29	19 (65.5)	26	18 (69.2)	0.95 [0.66; 1.37]; 0.790
GALAXI 2/3	140	92 (65.7)	140	83 (59.3)	1.11 [0.93; 1.33]; 0.250
Total[d]					1.08 [0.92; 1.27]; 0.366

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

Outcome category outcome study	Guselkumab		Ustekinumab		Guselkumab vs. ustekinumab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Absence of fistula[g]					
GALAXI 1	29	23 (79.3)	26	22 (84.6)	0.94 [0.73; 1.20]; 0.601
GALAXI 2/3	140	112 (80.0)	140	120 (85.7)	0.93 [0.84; 1.04]; 0.203
Total[d]					0.93 [0.85; 1.03]; 0.173
Fatigue (PROMIS Fatigue SF 7a – improvement[h])					
GALAXI 1 (improvement by ≥ 8.07 points)	29	16 (55.2)	26	13 (50.0)	1.11 [0.68; 1.83]; 0.680
GALAXI 2/3 (improvement by ≥ 9 points)	140	63 (45.0)	140	61 (43.6)	1.04 [0.80; 1.35]; 0.790
Total					1.05 [0.84; 1.33]; 0.651[i]
Symptoms – Improvement					
PGIC[j]					
GALAXI 1	29	25 (86.2)	26	24 (92.3)	0.93 [0.78; 1.12]; 0.464
GALAXI 2/3	No suitable data[k]				
PGIS[l]					
GALAXI 1	29	18 (62.1)	26	15 (57.7)	1.08 [0.70; 1.66]; 0.718
GALAXI 2/3	No suitable data[k]				
Health status (EQ-5D VAS – improvement[m])					
GALAXI 1	29	20 (69.0)	26	12 (46.2)	1.50 [0.93; 2.42]; 0.099
GALAXI 2/3	140	78 (55.7)	140	81 (57.9)	0.97 [0.79; 1.19]; 0.758
Total[d]					1.03 [0.86; 1.25]; 0.721
Activity impairment (WPAI-CD Item 6)	No suitable data[k]				
Health-related quality of life (at Week 48)					
IBDQ total score (improvement[n])					
GALAXI 1	29	18 (62.1)	26	18 (69.2)	0.90 [0.63; 1.30]; 0.589
GALAXI 2/3	140	92 (65.7)	140	87 (62.1)	1.06 [0.89; 1.26]; 0.503
Total[d]					1.03 [0.88; 1.21]; 0.729
Bowel symptoms[e]					
GALAXI 1	29	22 (75.9)	26	19 (73.1)	1.04 [0.76; 1.42]; –
GALAXI 2/3	140	95 (67.9)	140	96 (68.6)	0.99 [0.85; 1.16]; –
Total[d]					1.00 [0.87; 1.15]; –

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

Outcome category outcome study	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Systemic symptoms[i]					
GALAXI 1	29	19 (65.5)	26	18 (69.2)	0.95 [0.66; 1.37]; –
GALAXI 2/3	140	92 (65.7)	140	83 (59.3)	1.11 [0.93; 1.33]; –
Total[d]					1.08 [0.92; 1.27]; –
Emotional functioning[n]					
GALAXI 1	29	16 (55.2)	26	15 (57.7)	0.97 [0.65; 1.46]; –
GALAXI 2/3	140	81 (57.9)	140	80 (57.1)	1.02 [0.83; 1.24]; –
Total[d]					1.00 [0.83; 1.21]; –
Social functioning[n]					
GALAXI 1	29	16 (55.2)	26	19 (73.1)	0.76 [0.51; 1.13]; –
GALAXI 2/3	140	87 (62.1)	140	89 (63.6)	0.98 [0.82; 1.17]; –
Total[d]					0.94 [0.79; 1.10]; –
PROMIS-29 – Improvement[o]					
Physical Component Summary (PHS)					
GALAXI 1	No suitable data[k]				
GALAXI 2/3	140	71 (50.7)	140	59 (42.1)	1.20 [0.94; 1.55]; 0.151
Mental Component Summary (MHS)					
GALAXI 1	No suitable data[k]				
GALAXI 2/3	140	74 (52.9)	140	75 (53.6)	0.99 [0.80; 1.23]; 0.945
Physical functioning					
GALAXI (improvement by ≥ 5.10 points)	29	14 (48.3)	26	7 (26.9)	1.81 [0.87; 3.74]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	68 (48.6)	140	55 (39.3)	1.24 [0.95; 1.62]; –
Anxiety					
GALAXI (improvement by ≥ 6.20 points)	29	17 (58.6)	26	8 (30.8)	1.92 [1.00; 3.67]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	53 (37.9)	140	51 (36.4)	1.04 [0.77; 1.41]; –

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

Outcome category outcome study	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Depression					
GALAXI (improvement by ≥ 5.76 points)	29	15 (51.7)	26	7 (26.9)	1.96 [1.00; 3.84]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	53 (37.9)	140	46 (32.9)	1.17 [0.85; 1.60]; –
Fatigue					
GALAXI 1 (improvement by ≥ 6.32 points)	29	15 (51.7)	26	11 (42.3)	1.23 [0.70; 2.16]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	71 (50.7)	140	70 (50.0)	1.02 [0.81; 1.28]; –
Sleep interference					
GALAXI 1 (improvement by ≥ 6.20 points)	29	11 (37.9)	26	9 (34.6)	1.10 [0.55; 2.21]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	50 (35.7)	140	37 (26.4)	1.36 [0.95; 1.94]; –
Participation in social roles and activities					
GALAXI 1 (improvement by ≥ 5.51 points)	29	16 (55.2)	26	13 (50.0)	1.11 [0.68; 1.82]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	64 (45.7)	140	73 (52.1)	0.88 [0.70; 1.12]; –
Pain interference					
GALAXI (improvement by ≥ 5.10 points)	29	21 (72.4)	26	16 (61.5)	1.18 [0.82; 1.71]; –
GALAXI 2/3 (improvement by ≥ 7 points)	140	78 (55.7)	140	81 (57.9)	0.97 [0.79; 1.18]; –

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

Outcome category **outcome** **study**	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Pain intensity					
GALAXI (improvement by ≥ 3 points)	29	18 (62.1)	26	16 (61.5)	1.01 [0.67; 1.53]; –
GALAXI 2/3 (improvement by ≥ 3 points)	140	75 (53.6)	140	82 (58.6)	0.91 [0.75; 1.12]; –
Total[d]					0.93 [0.77; 1.12]; –
Side effects (up to Week 48)[p]					
AEs (supplementary information)					
GALAXI 1	35	24 (68.6)	30	22 (73.3)	–
GALAXI 2/3	140	98 (70.0)	140	98 (70.0)	–
SAEs					
GALAXI 1	35	3 (8.6)	30	2 (6.7)	1.28 [0.23; 7.21]; 0.777
GALAXI 2/3	140	11 (7.9)	140	13 (9.3)	0.82 [0.38; 1.80]; 0.627
Total[d]					0.91 [0.45; 1.83]; 0.788
Discontinuation due to AEs					
GALAXI 1	35	2 (5.7)	30	1 (3.3)	1.70 [0.16; 17.72]; 0.657
GALAXI 2/3	140	6 (4.3)	140	6 (4.3)	1.01 [0.34; 3.03]; 0.988
Total[d]					1.11 [0.41; 3.00]; 0.839
Infections[q]					
GALAXI 1	35	11 (31.4)	30	13 (43.3)	0.72 [0.38; 1.37]; 0.324
GALAXI 2/3	140	62 (44.3)	140	57 (40.7)	1.09 [0.83; 1.44]; 0.528
Total[d]					1.02 [0.79; 1.31]; 0.900

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

Outcome category outcome study	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**

a. RR, CI and p-value at study level: CMH method; stratified by
- GALAXI 1: CDAI score at baseline (≤ 300 or > 300).
- GALAXI 2/3: CDAI score at baseline (≤ 300 or > 300), SES-CD score at baseline (≤ 12 or > 12) and treatment with corticosteroids at baseline (yes/no).

In the categories morbidity and health-related quality of life, missing values were imputed using NRI.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Predefined as daily average SF ≤ 3 and daily average AP ≤ 1 at Week 48. At the same time, both values at Week 48 were not allowed to be worse than at baseline. In addition, for corticosteroid-free remission, the patient must not have been treated with corticosteroids for at least 90 days prior to Week 48. At Week 48, 69.0% patients in the intervention arm versus 73.1% in the control arm of GALAXI 1, and 77.9% patients in the intervention arm versus 75.7% in the control arm of GALAXI 2/3 had a daily average SF ≤ 3. 72.4% of patients in the intervention arm versus 84.6% in the control arm of GALAXI 1, and 72.9% of patients in the intervention arm versus 76.4% in the control arm of GALAXI 2/3 had a daily average AP ≤ 1 at Week 48. Data for the relevant subpopulation pertaining to the 90-day steroid-free status prior to Week 48 are not available. Based on the patients in the primary analysis population of the respective study who were being treated with oral corticosteroids (including budesonide/beclomethasone) at the start of the study, the proportion of patients who had a steroid-free status for at least 90 days prior to Week 48 was as follows (guselkumab vs. ustekinumab): GALAXI 1: 67% vs. 62%; GALAXI 2: 70% vs. 57%; GALAXI 3: 69% vs. 72%.
d. Meta-analysis, fixed-effect model (Mantel-Haenszel method); the meta-analysis of the company is not based on the reported study results from the respective CMH analysis with stratification, but on the unstratified 2×2 tables for GALAXI 1 and GALAXI 2/3.
e. A score increase by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 10 to 70).
f. A score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 5 to 35).
g. Defined as the complete absence of open or draining fistulae at Week 48.
h. A score decrease by ≥ 8.07 points from baseline is considered a clinically relevant improvement (scale range: 29.4 to 83.2).
i. Meta-analysis; Institute's calculation: fixed-effect model (inverse variance).
j. Defined as any improvement ("very much improved", "much improved" or "slightly improved").
k. See Section I 4.2.1 of the present dossier assessment for the reasoning.
l. Defined as any improvement in symptom severity on a five-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe") compared to baseline.
m. A score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
n. A score increase by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 32 to 224 [total score], 12 to 84 [emotional functioning] and 5 to 35 [social functioning]).
o. An increase in PHS by ≥ 6.12 points or in MHS by ≥ 6.42 points from baseline is considered a clinically relevant improvement (scale range: 21.6 to 62.4 for PHS and 19.5 to 62.3 for MHS; determined using the 2018 sample by Hays et al. [25]). For both the PHS and MHS of PROMIS-29 v2.0, 7 points are an appropriate approximation for a response criterion of 15% of the scale range (for the rationale, see Section I 4.2.1 of this benefit assessment).
p. Overall rate excluding disease-related events (see Section I 4.2.1 of this dossier assessment for explanation).
q. Operationalized as infections and infestations (SOC, AEs).

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

Outcome category **outcome** **study**	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary score; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NRI: non-responder imputation; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PHS: Physical Health Summary score; PRO2: patient-reported outcome 2; PROMIS: Patient-Reported Outcome Measurement Information System; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency; S7a: Short Form 7a; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease					

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

Mortality

The results on all-cause mortality were based on data on fatal AEs. There were no deaths in either GALAXI 1 or GALAXI 2/3. There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Corticosteroid-free remission (PRO2), bowel symptoms (IBDQ), systemic symptoms (IBDQ), absence of fistula, fatigue (PROMIS Fatigue SF7a), symptoms (PGIC, PGIS) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcomes corticosteroid-free remission (recorded using PRO2), bowel symptoms and systemic symptoms (each recorded using the IBDQ), absence of fistula, fatigue (recorded using PROMIS Fatigue SF7a), symptoms (recorded using PGIC and PGIS) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven in each case.

Activity impairment (WPAI-CD Item 6)

No suitable data are available for the outcome activity impairment (recorded using WPAI-CD item 6) (see Section I 4.2.1 for reasons). There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

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

PROMIS-29 Physical Component Summary (PCS) and Mental Component Summary (PCS)

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using PROMIS-29). There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs and infections (AEs)

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

I 4.2.4 Subgroups and other effect modifiers

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

- Age (≤ median/> median)
- Sex (male/female)
- CDAI total score at baseline (≤ 300/> 300)

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

Irrespective of this, an effect modification by the characteristic of CDAI total score at baseline was shown only for the outcome health-related quality of life (physical sum score, PROMIS-29), for which only a result from GALAXI 2/3 is available.

I 4.3 Probability and extent of added benefit

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

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

I 4.3.1 Assessment of added benefit at outcome level

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

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

Outcome category **outcome**	**Guselkumab vs. ustekinumab** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0--0 vs. 0--0[c] RR: –	Lesser benefit/added benefit not proven
Morbidity		
Corticosteroid-free remission at Week 48 (PRO2)	51.7–62.9 vs. 64.3–65.4[c] RR: 0.95 [0.80; 1.12]; p = 0.516	Lesser benefit/added benefit not proven
Bowel symptoms (IBDQ – improvement at Week 48)	67.9–75.9 vs. 68.6–73.1[c] RR: 1.00 [0.87; 1.15]; p = 0.978	Lesser benefit/added benefit not proven
Systemic symptoms (IBDQ – improvement at Week 48)	65.5–65.7 vs. 59.3–69.2[c] RR: 1.08 [0.92; 1.27]; p = 0.366	Lesser benefit/added benefit not proven
Absence of fistula	79.3–80.0 vs. 84.6–85.7[c] RR: 0.93 [0.85; 1.03]; p = 0.173	Lesser benefit/added benefit not proven

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

Outcome category outcome	**Guselkumab vs. ustekinumab proportion of events (%) effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
Fatigue (PROMIS Fatigue SF7a – improvement at Week 48)	45.0–55.2 vs. 43.6–50.0[c] RR: 1.05 [0.84; 1.33]; p = 0.651	Lesser benefit/added benefit not proven
Symptoms (PGIC – improvement at Week 48)[d]	86.2 vs. 92.3 RR: 0.93 [0.78; 1.12]; p = 0.464	Lesser benefit/added benefit not proven
Symptoms (PGIS – improvement at Week 48)[d]	62.1 vs. 57.7 RR: 1.08 [0.70; 1.66]; p = 0.718	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS – improvement at Week 48)	55.7–69.0 vs. 46.2–57.9[c] RR: 1.03 [0.86; 1.25]; p = 0.721	Lesser benefit/added benefit not proven
Activity impairment (WPAI-CD Item 6)	No suitable data[e]	Lesser benefit/added benefit not proven
Health-related quality of life		
IBDQ total score (improvement at Week 48)	62.1–65.7 vs. 62.1–69.2[c] RR: 1.03 [0.88; 1.21]; p = 0.729	Lesser benefit/added benefit not proven
PROMIS-29 Physical Health Summary score (PHS) - improvement at Week 48[f]	50.7 vs. 42.1 RR: 0.99 [0.94; 1.55]; p = 0.151	Lesser benefit/added benefit not proven
PROMIS-29 Mental Health Summary score (MHS) - improvement at Week 48[f]	52.9 vs. 53.6 RR: 0.99 [0.80; 1.23]; p = 0.945	Lesser benefit/added benefit not proven
Side effects		
SAEs	7.9–8.6 vs. 6.7–9.3[c] RR: 0.91 [0.45; 1.83]; p = 0.788	Lesser benefit/added benefit not proven
Discontinuation due to AEs	4.3–5.7 vs. 3.3–4.3[c] RR: 1.11 [0.41; 3.00]; p = 0.839	Lesser benefit/added benefit not proven
Infections (AEs)	31.4–44.3 vs. 40.7–43.3[c] RR: 1.02 [0.79; 1.31]; p = 0.900	Lesser benefit/added benefit not proven

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

Outcome category outcome	**Guselkumab vs. ustekinumab proportion of events (%) effect estimation [95% CI]; p-value probability[a]**	**Derivation of extent[b]**
a. Probability provided if statistically significant differences are present. 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. Minimum and maximum proportions of events in each treatment arm in the studies included. d. Usable data only available in GALAXI 1; for reasoning, see Section I 4.2.1 of the present dossier assessment. e. See Section I 4.2.1 of this dossier assessment for the reasoning. f. Suitable data are only available in GALAXI 2/3; for reasoning, see Section I 4.2.1 of this dossier assessment. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PHS: Physical Health Summary Score; PRO2: Patient-Reported Outcome 2; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF7a: Short Form 7a; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease		

I 4.3.2 Overall conclusion on added benefit

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

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

Positive effects	**Negative effects**
–	–
Data for the outcome activity impairment (WPAI-CD Item 6) are missing.	
WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease	

For research question 1 of this benefit assessment, neither positive nor negative effects of guselkumab compared with ustekinumab were shown in the relevant subpopulation.

In summary, there is no hint of an added benefit of guselkumab over ustekinumab for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy. An added benefit is therefore not proven.

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

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

I 5.1 Study characteristics (specific to research question 2)

For characteristics of the studies that apply to all research questions, see Section I 3.2.

I 5.1.1 Patient characteristics

Table 16 shows the characteristics of the patients in the subpopulation relevant to research question 2 in the studies included.

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

Study characteristic category	GALAXI 1		GALAXI 2/3	
	guselkumab	ustekinumab	guselkumab	ustekinumab
	N[a] = 32	N[a] = 37	N[b] = 157	N[b] = 160
Age [years]				
Mean (SD)	41 (13)	36 (13)	35 (12)	39 (13)
Median [Q1; Q3]	41 [31; 49]	35 [25; 40]	33 [27; 43][c]	38 [28; 48][d]
Sex [F/M], %	41/59	41/59	45/55	41/59
Region, n (%)				
Asia	4 (13)	5 (14)	49 (31)	42 (26)
Eastern Europe	11 (34)	18 (49)	35 (22)	36 (23)
North America	9 (28)	6 (16)	14 (9)	24 (15)
Rest of the world	8 (25)	8 (22)	59 (38)	58 (36)
Time since diagnosis of Crohn's disease [months]				
Median [Q1; Q3]	8.7 [5.3; 16.6]	6.3 [3.4; 10.4]	6.9 [3.3; 12.2]	6.2 [3.4; 11.0]
Disease location[e], n (%)				
Ileum isolated	10 (31)	8 (22)	30 (19)	31 (19)
Colon isolated	12 (38)	15 (41)	58 (37)	37 (42)
Ileocolon	10 (31)	14 (38)	69 (44)	62 (39)
Fistulae, n (%)	11 (34)	16 (43)	53 (34)	41 (26)
≥ 1 open or draining fistula	5 (16[f])	5 (14[f])	24 (15[f])	14 (9[f])
SES-CD total score, mean (SD)	13.2 (9.0)	16.3 (9.0)	13.9 (7.8)	13.0 (6.9)
CDAI total score, mean (SD)	307.4 (62.0)	312.1 (63.3)	294.1 (53.2)	294.9 (51.4)

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

Study characteristic category	GALAXI 1		GALAXI 2/3	
	guselkumab	ustekinumab	guselkumab	ustekinumab
	N[a] = 32	N[a] = 37	N[b] = 157	N[b] = 160
PRO2 components, n (%)				
Stool frequency (CDAI-SF)				
Per day mean (SD)	6.2 (3.4)	5.5 (2.7)	4.6 (2.3)	5.0 (2.5)
> 3 per day, n (%)	27 (84)	33 (89)	116 (74)	124 (78)
Abdominal pain (CDAI-AP)				
Mean (SD)	1.9 (0.6)	1.9 (0.5)	2.0 (0.6)	2.0 (0.6)
> 1, n (%)	28 (88)	35 (95)	145 (92)	146 (91)
Stool frequency > 3 per day (CDAI-SF) and abdominal pain (CDAI-AP) > 1	23 (72)	31 (84)	104 (66)	110 (69)
IBDQ, mean (SD)				
IBDQ total score	128.9 (32.0)[g]	133.1 (33.6)[g]	123.3 (30.2)[g]	127.3 (31.9)[g]
IBDQ bowel symptoms	41.0 (9.7)[g]	40.8 (10.5)[g]	39.0 (9.3)[g]	39.7 (9.5)[g]
IBDQ systemic symptoms	17.2 (5.9)[g]	18.1 (6.8)[g]	16.7 (5.4)[g]	16.8 (5.5)[g]
PROMIS-29 at baseline, mean (SD)				
Physical Component Summary (PHS)	ND	ND	43.0 (8.5)[g]	44.0 (7.8)[g]
Mental Component Summary (MHS)	ND	ND	42.3 (7.1)[g]	42.7 (7.8)[g]
PROMIS Fatigue SF7a, mean (SD)	58.3 (8.6)[g]	58.2 (7.7)[g]	59.6 (7.6)[g]	58.5 (7.6)[g]
EQ-5D VAS, mean (SD)	51.7 (18.5)[g]	49.4 (20.5)[g]	49.8 (19.7)[g]	51.5 (18.8)[g]
PGIS, mean (SD)	3.7 (0.8)[g]	3.6 (0.8)[g]	3.7 (0.7)[g]	3.5 (0.7)[g]
Primary or secondary non-response or intolerance to anti-TNF agents, n (%)	30 (94)	37 (100)	152 (97)	151 (94)
Primary or secondary non-response or intolerance to vedolizumab, n (%)	6 (19)	5 (14)	25 (16)	33 (21)
Treatment discontinuation, n (%)	5 (16)[h]	6 (16)[h]	24 (15)[i, j]	32 (20)[i, j]
Study discontinuation, n (%)	2 (6)[k]	2 (5)[k]	16 (10)[l, m]	14 (9)[l, m]

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

Study characteristic category	GALAXI 1		GALAXI 2/3	
	guselkumab	ustekinumab	guselkumab	ustekinumab
	N[a] = 32	N[a] = 37	N[b] = 157	N[b] = 160

a. Number of randomized patients in subpopulation B whose treatment was not discontinued during the induction phase as a result of the safety measure (primary analysis population. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Median [Q1; Q3] in GALAXI 2: 33 [28; 43]; in GALAXI 3: 33 [25; 44].
d. Median [Q1; Q3] in GALAXI 2: 38 [27; 48]; in GALAXI 3: 38 [29; 48].
e. Based on a central assessment.
f. Institute's calculation.
g. Module 4 B contains varying information regarding the baseline values. The values in the table correspond to Module 4 B, Section 4.3.1.3, and are based on the patients for whom values were available at the start of the study. In GALAXI 1, there were 31 versus 36 patients for the IBDQ, PROMIS Fatigue SF7a and EQ-5D VAS, and 31 versus 37 patients for the PGIS; in GALAXI 2/3, there were 155 vs. 155 patients each for IBDQ, PROMIS-29 and PROMIS Fatigue SF7a; 154 vs. 153 patients for EQ-5D VAS, and 156 vs. 155 patients for PGIS.
h. In GALAXI 1, reasons for discontinuation of treatment in the intervention versus the control arm (percentages refer to the primary analysis population) were: worsening of the disease (3% vs. 8%), AEs (3% vs. 3%), lack of efficacy (3% vs. 0%), patient request (3% vs. 0%), lost to follow-up (3% vs. 0%), pregnancy (0% vs. 3%), other reasons (0% vs. 3%).
i. Institute's calculation; 12 (15%) patients in the intervention arm versus 12 (15%) in the comparator arm of GALAXI 2, and 12 (15%) versus 20 (26%) patients in the intervention arm of GALAXI 3 discontinued treatment.
j. Reasons for treatment discontinuation in the intervention versus the control arm (percentages based on randomized patients in subpopulation B) in GALAXI 2: patient request (4% vs. 5%), lack of efficacy (4% vs. 2%), worsening of the disease (3% vs. 2%), AEs (3% vs. 2%), pregnancy (1% vs. 0%), other reasons (1% vs. 0%); in GALAXI 3: lack of efficacy (4% vs. 8%), worsening of the disease (1% vs. 6%), AEs (3% vs. 4%), patient request (4% vs. 3%), pregnancy (3% vs. 0%), initiation of a disallowed concomitant treatment (0% vs. 1%), other reasons (1% vs. 1%).
k. Reasons for study discontinuation in the intervention versus the control arm were the following (percentages based on the primary analysis population): in GALAXI 1: patient request (3% vs. 3%), lost-to-follow-up (3% vs. 0%), other reasons (0% versus 3%).
l. Institute's calculation; in GALAXI 2, 6 (8%) patients in the intervention arm versus 5 (6%) patients in the comparator arm, and 10 (13%) versus 9 (12%) patients in the intervention arm of GALAXI 3 discontinued treatment.
m. In GALAXI 2, reasons for study discontinuation in the intervention versus the control arm (percentages based on randomized patients in subpopulation B) were: patient request (6% vs. 5%), lost to follow-up (0% vs. 1%), other reasons (1% vs. 0%); in GALAXI 3: patient request (13% vs. 12%).

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; F: female; IBDQ: Inflammatory Bowel Disease Questionnaire; M: male; MHS: Mental Health Summary score (Mental Component Summary); n: number of patients in the category; N: number of analysed patients; ND: no data; PGIC: Patient Global Impression of Change; PHS: Physical Health Summary score (Physical Component Summary); PGIS: Patient Global Impression of Severity; PRO2: patient-reported outcome 2; PROMIS: Patient-Reported Outcome Measurement Information System; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency; SF7a: Short Form 7a; VAS: visual analogue scale

The median age of the patients in the subpopulation not eligible for a biologic agent ranged between 33 and 41 years. They had been diagnosed with Crohn's disease for a median of 6.2 to 8.7 years. Patients from the category *Rest of the world* (including Germany) were the most numerous across all studies; they accounted for between 22% and 38%. Across all studies, patients from Eastern Europe accounted for a smaller proportion, and the fewest came from North America. The majority of patients (74% to 89%) had a daily average SF > 3 (as measured by the CDAI-SF), and almost all of them reported abdominal pain > 1 (recorded with the CDAI-AP, scale range 0 = no pain to 3 = strong pain).

In almost all patients, pretreatment with anti-TNF agents had failed; the proportion of patients in whom treatment with vedolizumab failed ranged from 14% to 21%.

The proportions of patients who discontinued treatment or the study were similarly high in both arms in GALAXI 1 and GALAXI 2/3 (15% to 20% with treatment discontinuation, and 5% to 6% for study discontinuation). The most common reasons for discontinuing treatment across all studies were lack of efficacy, worsening of the disease and patient request; the most common reason for study discontinuation across all studies was patient request.

Overall, the demographic and clinical characteristics of the patients included are considered to be sufficiently comparable.

I 5.1.2 Concomitant treatments

Concomitant treatments with corticosteroids and/or immunosuppressants at baseline or during the course of the study are shown in Table 17.

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

Study time point drug class drug	Patients with concomitant therapy n (%)	
	guselkumab	ustekinumab
GALAXI 1	N = 32	N = 37
Concomitant treatments at baseline	19 (59)	27 (73)
Oral corticosteroids	9 (28)	13 (35)
Oral corticosteroids (excluding budesonide/beclomethasone)	7 (22)	10 (27)
Budesonide	2 (6)	3 (8)
Beclomethasone	0 (0)	0 (0)
Immunosuppressants	9 (28)	11 (30)
Azathioprine or 6-mercaptopurine	7 (22)	10 (27)
Methotrexate	2 (6)	1 (3)
Concomitant treatments during the study	ND	ND
GALAXI 2/3	N = 157	N = 160
Concomitant treatments at baseline	95 (61)	104 (65)
Oral corticosteroids	46 (29)	47 (29)
Oral corticosteroids (excluding budesonide/beclomethasone)	39 (25)	38 (24)
Budesonide	7 (4)	9 (6)
Beclomethasone	0 (0)	0 (0)
Immunosuppressants	44 (28)	48 (30)
Azathioprine or 6-mercaptopurine	41 (26)	44 (28)
Methotrexate	3 (2)	4 (3)
Concomitant treatments during the study	ND	ND

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

More than half of the study populations were receiving concomitant therapy at the start of the study. The proportion of patients receiving concomitant therapy with corticosteroids and/or immunosuppressants at baseline was around 30% and was balanced between the study arms. Information on concomitant therapies during the study is not available. However, the protocol included guidelines on concomitant treatment (see Table 7).

I 5.1.3 Risk of bias across outcomes (study level)

The risk of bias across outcomes is described in Table 10 in Section I 4.1.3 for both studies and was rated as low.

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

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

I 5.2 Results on added benefit

I 5.2.1 Outcomes included

The patient-relevant outcomes that were to be included in the assessment were identical for research questions 1 and 2 and can be found in Section I 4.2.1. Table 11 shows for which outcomes data were available in the included studies.

I 5.2.2 Risk of bias

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

I 5.2.3 Results

Table 18 summarizes the results of the comparison of guselkumab with ustekinumab in adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The forest plots of the meta-analyses calculated by the Institute can be found in Appendix D.2 of the full dossier assessment.

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

Outcome category outcome study	Guselkumab		Ustekinumab		Guselkumab vs. ustekinumab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Mortality (until Week 48)					
All-cause mortality[b]					
GALAXI 1	38	0 (0)	41	0 (0)	–
GALAXI 2/3	157	0 (0)	160	0 (0)	–
Total					–
Morbidity (at Week 48)					
Corticosteroid-free remission (PRO2)[c]					
GALAXI 1	32	17 (53.1)	37	15 (40.5)	1.34 [0.76; 2.34]; 0.311
GALAXI 2/3	157	87 (55.4)	160	73 (45.6)	1.21 [0.97; 1.50]; 0.085
Total[d]					1.23 [1.01; 1.50]; 0.044
Remission (PRO2)[c] (supplementary presentation)					
GALAXI 1	*32*	*17 (53.1)*	*37*	*15 (40.5)*	*1.31 [0.79; 2.19]; 0.294*
GALAXI 2/3	*157*	*91 (58.0)*	*160*	*81 (50.6)*	*1.14 [0.93; 1.40]; 0.197*
Total[d]					*1.17 [0.97; 1.41]; 0.104*
Bowel symptoms (IBDQ – improvement)e					
GALAXI 1	32	19 (59.4)	37	23 (62.2)	0.95 [0.65; 1.40]; 0.808
GALAXI 2/3	157	101 (64.3)	160	84 (52.5)	1.22 [1.01; 1.47]; 0.043
Total[d]					1.17 [0.99; 1.38]; 0.067
Systemic symptoms (IBDQ – improvement)f					
GALAXI 1	32	18 (56.3)	37	22 (59.5)	0, 95 [0.63; 1.43]; 0.790
GALAXI 2/3	157	89 (56.7)	160	83 (51.9)	1.09 [0.89; 1.33]; 0.429
Total[d]					1.06 [0.89; 1.27]; 0.505
Absence of fistula[g]					
GALAXI 1	32	22 (68.8)	37	25 (67.6)	1.02 [0.73; 1.42]; 0.919
GALAXI 2/3	157	117 (74.5)	160	117 (73.1)	1.02 [0.89; 1.16]; 0.802
Total[d]					1.02 [0.90; 1.15]; 0.764
Fatigue (PROMIS Fatigue SF 7a – improvement[h])					
GALAXI (improvement by ≥ 8.07 points)	32	14 (43.8)	37	14 (37.8)	1.15 [0.65; 2.05]; 0.632
GALAXI 2/3 (improvement by ≥ 9 points)	157	60 (38.2)	160	47 (29.4)	1.30 [0.95; 1.78]; 0.101
Total					1.26 [0.96; 1.66]; 0.096[i]

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

Outcome category **outcome** **study**	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Symptoms – Improvement					
PGIC[j]					
GALAXI 1	32	24 (75.0)	37	23 (62.2)	1, 21 [0.88; 1.67]; 0.245
GALAXI 2/3	No suitable data[k]				
PGIS[l]					
GALAXI 1	32	20 (62.5)	37	18 (48.6)	1.28 [0.84; 1.97]; 0.251
GALAXI 2/3	No suitable data[k]				
Health status (EQ-5D-VAS – improvement[m])					
GALAXI 1	32	19 (59.4)	37	20 (54.1)	1.10 [0.72; 1.67]; 0.659
GALAXI 2/3	157	83 (52.9)	160	79 (49.4)	1.07 [0.86; 1.33]; 0.544
Total[d]					1.08 [0.89; 1.30]; 0.453
Activity impairment (WPAI-CD Item 6)	No suitable data[j]				
Health-related quality of life (Week 48)					
IBDQ total score (improvement[n])					
GALAXI 1	32	20 (62.5)	37	22 (59.5)	1.05 [0.72; 1.53]; 0.802
GALAXI 2/3	157	97 (61.8)	160	76 (47.5)	1.29 [1.05; 1.59]; 0.015
Total[d]					1.25 [1.04; 1.49]; 0.016
Bowel symptoms[e]					
GALAXI 1	32	19 (59.4)	37	23 (62.2)	0.95 [0.65; 1.40]; –
GALAXI 2/3	157	101 (64.3)	160	84 (52.5)	1.22 [1.01; 1.47]; –
Total[d]					1.17 [0.99; 1.38]; –
Systemic symptoms[f]					
GALAXI 1	32	18 (56.3)	37	22 (59.5)	0.95 [0.63; 1.43]; –
GALAXI 2/3	157	89 (56.7)	160	83 (51.9)	1.09 [0.89; 1.33]; –
Total[d]					1.06 [0.89; 1.27]; –
Emotional functioning[n]					
GALAXI 1	32	17 (53.1)	37	23 (62.2)	0.85 [0.56; 1.29]; –
GALAXI 2/3	157	87 (55.4)	160	65 (40.6)	1.36 [1.08; 1.73]; –
Total[d]					1.24 [1.01; 1.52]; –

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

Outcome category outcome study	Guselkumab		Ustekinumab		Guselkumab vs. ustekinumab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Social functioning[n]					
GALAXI 1	32	20 (62.5)	37	23 (62.2)	1.00 [0.69; 1.46]; –
GALAXI 2/3	157	96 (61.1)	160	78 (48.8)	1.24 [1.02; 1.52]; –
Total[d]					1.20 [1.01; 1.43]; –
PROMIS-29 – Improvement[o]					
Physical Component Summary (PHS)					
GALAXI 1	No suitable data[n]				
GALAXI 2/3	157	57 (36.3)	160	56 (35.0)	1.04 [0.77; 1.41]; 0.810
Mental Health Summary score (MHS)					
GALAXI 1	No suitable data[n]				
GALAXI 2/3	157	73 (46.5)	160	61 (38.1)	1.22 [0.93; 1.58]; 0.150
Physical functioning					
GALAXI (improvement by ≥ 5.10 points)	32	12 (37.5)	37	11 (29.7)	1.25 [0.65; 2.42]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	55 (35.0)	160	52 (32.5)	1.08 [0.79; 1.48]; –
Anxiety					
GALAXI (improvement by ≥ 6.20 points)	32	8 (25.0)	37	16 (43.2)	0.58 [0.28; 1.17]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	53 (33.8)	160	55 (34.4)	0.98 [0.72; 1.34]; –
Depression					
GALAXI (improvement by ≥ 5.76 points)	32	11 (34.4)	37	17 (45.9)	0.75 [0.41; 1.36]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	49 (31.2)	160	44 (27.5)	1.14 [0.81; 1.60]; –
Fatigue					
GALAXI 1 (improvement by ≥ 6.32 points)	32	20 (62.5)	37	18 (48.6)	1.29 [0.84; 1.98]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	71 (45.2)	160	61 (38.1)	1.18 [0.91; 1.54]; –

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

Outcome category outcome study	Guselkumab		Ustekinumab		Guselkumab vs. ustekinumab
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Sleep interference					
GALAXI 1 (improvement by ≥ 6.20 points)	32	11 (34.4)	37	12 (32.4)	1.06 [0.54; 2.08]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	40 (25.5)	160	41 (25.6)	1.00 [0.68; 1.46]; –
Participation in social roles and activities					
GALAXI 1 (improvement by ≥ 5.51 points)	32	14 (43.8)	37	20 (54.1)	0.81 [0.49; 1.34]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	64 (40.8)	160	60 (37.5)	1.08 [0.82; 1.43]; –
Pain interference					
GALAXI (improvement by ≥ 5.10 points)	32	18 (56.3)	37	20 (54.1)	1.04 [0.68; 1.58]; –
GALAXI 2/3 (improvement by ≥ 7 points)	157	76 (48.4)	160	71 (44.4)	1.09 [0.85; 1.39]; –
Pain intensity					
GALAXI 1 (improvement by ≥ 3 points)	32	16 (50.0)	37	18 (48.6)	1.03 [0.62; 1.68]; –
GALAXI 2/3 (improvement by ≥ 3 points)	157	82 (52.2)	160	70 (43.8)	1.19 [0.94; 1.50]; –
Total[d]					1.16 [0.94; 1.43]; –
Side effects (up to Week 48)[p]					
AEs (supplementary information)					
GALAXI 1	38	28 (73.7)	41	32 (78.0)	–
GALAXI 2/3	156	117 (75.0)	160	120 (75.0)	–
SAEs					
GALAXI 1	38	3 (7.9)	41	4 (9.8)	0.78 [0.19; 3.21]; 0.734
GALAXI 2/3	156	12 (7.7)	160	17 (10.6)	0.72 [0.35; 1.48]; 0.379
Total[d]					0.74 [0.39; 1.39]; 0.350

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

Outcome category outcome study	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Discontinuation due to AEs					
GALAXI 1	38	1 (2.6)	41	1 (2.4)	1.00 [0.07; 14.85]; 1.000
GALAXI 2/3	156	9 (5.8)	160	7 (4.4)	1.38 [0.53; 3.56]; 0.512
Total[d]					1.29 [0.52; 3.20]; 0.583
Infections[q]					
GALAXI 1	38	12 (31.6)	41	13 (31.7)	0.98 [0.52; 1.88]; 0.962
GALAXI 2/3	156	65 (41.7)	160	69 (43.1)	0.97 [0.76; 1.26]; 0.844
Total[d]					0.97 [0.76; 1.23]; 0.808

a. RR, CI and p-value at study level: CMH method; stratified by
- GALAXI 1: CDAI score at baseline (≤ 300 or > 300).
- GALAXI 2/3: CDAI score at baseline (≤ 300 or > 300), SES-CD score at baseline (≤ 12 or > 12) and treatment with corticosteroids at baseline (yes/no).

In the categories morbidity and health-related quality of life, missing values were imputed using NRI.
b. The results on all-cause mortality are based on the data on fatal AEs.
c. Predefined as daily average SF ≤ 3 and daily average AP ≤ 1 at Week 48. At the same time, both values at Week 48 were not allowed to be worse than at baseline. In addition, for corticosteroid-free remission, the patient must not have been treated with corticosteroids for at least 90 days prior to Week 48. At Week 48, 62.5% patients in the intervention arm versus 56.8% in the control arm of GALAXI 1, and 71.3% patients in the intervention arm versus 61.9% in the control arm of GALAXI 2/3 had a daily average SF ≤ 3. 75.0% of patients in the intervention arm versus 48.6% in the control arm of GALAXI 1, and 65.0% of patients in the intervention arm versus 62.5% in the control arm of GALAXI 2/3 had a daily average AP ≤ 1 at Week 48. Data for the relevant subpopulation pertaining to the 90-day steroid-free status prior to Week 48 are not available. Based on the patients in the primary analysis population of the respective study who were being treated with oral corticosteroids (including budesonide/beclomethasone) at the start of the study, the proportion of patients who had a steroid-free status for at least 90 days prior to Week 48 was as follows (guselkumab vs. ustekinumab): GALAXI 1: 67% vs. 62%; GALAXI 2: 70% vs. 57%; GALAXI 3: 69% vs. 72%.
d. Meta-analysis, fixed-effect model (Mantel-Haenszel method); the meta-analysis of the company is not based on the reported study results from the respective CMH analysis with stratification, but on the unstratified 2×2 tables for GALAXI 1 and GALAXI 2/3.
e. A score increase by ≥ 9 points from baseline is considered a clinically relevant improvement (scale range: 10 to 70).
f. A score increase by ≥ 4.5 points from baseline is considered a clinically relevant improvement (scale range: 5 to 35).
g. Defined as the complete absence of open or draining fistulae at Week 48.
h. A score decrease by ≥ 8.07 points from baseline is considered a clinically relevant improvement (scale range: 29.4 to 83.2).
i. Meta-analysis; Institute's calculation: fixed-effect model (inverse variance).
j. Defined as any improvement ("very much improved", "much improved" or "slightly improved").
k. See Section I 4.2.1 of the present dossier assessment for the reasoning.
l. Defined as any improvement in symptom severity on a five-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe") compared to baseline.

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

Outcome category **outcome** **study**	**Guselkumab**		**Ustekinumab**		**Guselkumab vs. ustekinumab**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**

m. A score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).
n. A score increase by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 32 to 224 [total score], 12 to 84 [emotional functioning] and 5 to 35 [social functioning]).
o. An increase in PHS by ≥ 6.12 points or in MHS by ≥ 6.42 points from baseline is considered a clinically relevant improvement (scale range: 21.6 to 62.4 for PHS and 19.5 to 62.3 for MHS; determined using the 2018 sample by Hays et al. [25]). For both the PHS and MHS of PROMIS-29 v2.0, 7 points are an appropriate approximation for a response criterion of 15% of the scale range (for the rationale, see Section I 4.2.1 of this benefit assessment).
p. Overall rate excluding disease-related events (see Section I 4.2.1 of this dossier assessment for explanation).
q. Operationalized as infections and infestations (SOC, AEs).

AE: adverse event; AP: abdominal pain; CDAI: Crohn's Disease Activity Index; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary score; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NRI: non-responder imputation; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PHS: Physical Health Summary score; PRO2: patient-reported outcome 2; PROMIS: Patient-Reported Outcome Measurement Information System; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SES-CD: Simple Endoscopic Score for Crohn's Disease; SF: stool frequency; SF7a: Short Form 7a; SOC: System Organ Class; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

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

Mortality

The results on all-cause mortality were based on data on fatal AEs. There were no deaths in either GALAXI 1 or GALAXI 2/3. There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Corticosteroid-free remission (PRO2)

A statistically significant difference between the treatment groups in favour of guselkumab was found for the outcome corticosteroid-free remission (recorded using PRO2). However, the extent of the effect in this non-serious/non-severe outcome was no more than marginal. There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Bowel symptoms (IBDQ), systemic symptoms (IBDQ), absence of fistula, fatigue (PROMIS Fatigue SF7a), symptoms (PGIC, PGIS) and health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for each of the outcomes bowel symptoms and systemic symptoms (recorded using the IBDQ), absence of fistula, fatigue (recorded using the PROMIS Fatigue SF7a), symptoms (recorded using PGIC and PGIS) and health status (recorded using EQ-5D VAS). There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven in each case.

Activity impairment (WPAI-CD Item 6)

No suitable data are available for the outcome activity impairment (recorded using WPAI-CD item 6) (see Section I 4.2.1 for reasons). There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Health-related quality of life

IBDQ total score

A statistically significant difference between the treatment groups in favour of guselkumab was found for health-related quality of life (recorded using the IBDQ). There is a hint of minor added benefit of guselkumab in comparison with golimumab.

PROMIS-29 Physical Component Summary (PCS) and Mental Component Summary (PCS)

There was no statistically significant difference between the treatment groups for health-related quality of life (recorded using PROMIS-29). There was no hint of an added benefit of guselkumab in comparison with ustekinumab; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs and infections (AEs)

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

I 5.2.4 Subgroups and other effect modifiers

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

- Age (≤ median/> median)
- Sex (male/female)
- CDAI total score at baseline (≤ 300/> 300)

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

Irrespective of this, no relevant effect modification was identified in accordance with the methods described for the outcomes presented.

I 5.3 Probability and extent of added benefit

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

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

I 5.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 5.2.3 (see Table 19).

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.

Corticosteroid-free remission (PRO2)

For corticosteroid-free remission (PRO2), the mean values of the daily SF (CDAI-SF) were 5 to 6 and abdominal pain was 2 (CDAI-AP) on a scale of 0 to 3 (moderate) in the subpopulation of patients who were ineligible for a biologic agent at the start of the study. The company did not provide any information on the threshold value for a classification as severe/serious. Therefore, the outcome corticosteroid-free remission (PRO2) was assigned to the outcome category non-serious/non-severe symptoms/late complications.

Table 19: Extent of added benefit at outcome level: guselkumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Outcome category **outcome**	**Guselkumab vs. ustekinumab** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0--0 vs. 0--0[c] RR: –	Lesser benefit/added benefit not proven
Morbidity		
Corticosteroid-free remission at Week 48 (PRO2)	53.1–55.4 vs. 40.5–45.6[c] RR: 1.23 [1.01; 1.50] RR: 0.81 [0.67; 0.99][d]; p = 0.044 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.000$ added benefit not proven[e]
Bowel symptoms (IBDQ – improvement at Week 48)	59.4–64.3 vs. 52.5– 62.2[c] RR: 1.17 [0.99; 1.38]; p = 0.067	Lesser benefit/added benefit not proven
Systemic symptoms (IBDQ – improvement at Week 48)	56.3–56.7 vs. 51.9–59.5[c] RR: 1.06 [0.89; 1.27]; p = 0.505	Lesser benefit/added benefit not proven
Absence of fistula	68.8–74.5 vs. 67.6–73.1[c] RR: 1.02 [0.90; 1.15]; p = 0.764	Lesser benefit/added benefit not proven
Fatigue (PROMIS Fatigue SF7a – improvement at Week 48)	38.2–43.8 vs. 29.4–37.8[c] RR: 1.26 [0.96; 1.66]; p = 0.096	Lesser benefit/added benefit not proven
Symptoms (PGIC - improvement at Week 48)[f]	75.0 vs. 62.2 RR: 1.21 [0.88; 1.67]; p = 0.245	Lesser benefit/added benefit not proven
Symptoms (PGIS - improvement at Week 48)[f]	62.5 vs. 48.6 RR: 1.28 [0.84; 1.97]; p = 0.251	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS – improvement at Week 48)	52.9–59.4 vs. 49.4–54.1[c] RR: 1.08 [0.89; 1.30]; p = 0.453	Lesser benefit/added benefit not proven
Activity impairment (WPAI-CD Item 6)	No suitable data[g]	Lesser benefit/added benefit not proven

Table 19: Extent of added benefit at outcome level: guselkumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) (multipage table)

Outcome category **outcome**	**Guselkumab vs. ustekinumab** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
IBDQ total score (improvement at Week 48)	61.8–62.5 vs. 47.5–59.5[c] RR: 1.25 [1.04; 1.49] RR: 0.80 [0.67; 0.96][d]; p = 0.016 probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
PROMIS-29 Physical Health Summary score (PHS) - improvement at Week 48)[f]	36.3 vs. 35.0 RR: 1.04 [0.77; 1.41]; p = 0.810	Lesser benefit/added benefit not proven
PROMIS-29 Mental Health Summary score (MHS - improvement at Week 48)[h]	46.5 vs. 38.1 RR: 1.22 [0.93; 1.58]; p = 0.150	Lesser benefit/added benefit not proven
Side effects		
SAEs	7.7–7.9 vs. 9.8–10.6[c] RR: 0.74 [0.39; 1.39]; p = 0.350	Lesser benefit/added benefit not proven
Discontinuation due to AEs	2.6–5.8 vs. 2.4–4.4[c] RR: 1.29 [0.52; 3.20]; p = 0.583	Lesser benefit/added benefit not proven
Infections (AEs)	31.6–41.7 vs. 31.7–43.1[c] RR: 0.97 [0.76; 1.23]; p = 0.808	Lesser benefit/added benefit not proven

a. Probability provided if statistically significant differences are present.
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. Minimum and maximum proportions of events in each treatment arm in the studies included.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Suitable data only available in GALAXI 1; for reasoning, see Section I 4.2.1 of this dossier assessment.
g. See Section I 4.2.1 of the present dossier assessment for the reasoning.
h. Suitable data are only available in GALAXI 2/3; for reasoning, see Section I 4.2.1 of this dossier assessment.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; IBDQ: Inflammatory Bowel Disease Questionnaire; MHS: Mental Health Summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PHS: Physical Health Summary Score; PRO2: Patient-Reported Outcome 2; PROMIS: Patient-Reported Outcomes Measurement Information System; RR: relative risk; SAE: serious adverse event; SF7a: Short Form 7a; VAS: visual analogue scale; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

I 5.3.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 20: Positive and negative effects from the assessment of guselkumab in comparison with ustekinumab (research question 2: patients who are not eligible for a biologic agent)

Positive effects	Negative effects
Health-related quality of life ▪ IBDQ total score: hint of added benefit – extent: "minor"	–
Data for the outcome activity impairment (WPAI-CD Item 6) are missing.	
IBDQ: Inflammatory Bowel Disease Questionnaire; WPAI-CD: Work Productivity and Activity Impairment Questionnaire – Crohn's Disease	

For research question 2 of this benefit assessment, a positive effect of guselkumab compared to ustekinumab was shown in the relevant subpopulation. For the outcome health-related quality of life, operationalized as an improvement in the IBDQ total score, there is a hint of added with the extent "minor". In summary, there is a hint of minor added benefit of guselkumab over ustekinumab for adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNFα antagonist or integrin inhibitor or interleukin inhibitor).

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

I 6 Probability and extent of added benefit – summary

Table 21 presents a summary of the probability and extent of the added benefit of guselkumab in comparison with the ACT.

Table 21: Guselkumab – probability and extent of added benefit

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

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. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
c. Continuation of an inadequate therapy does not concur with the specified ACT.
d. The GALAXI studies did not include any patients who had previously been treated with an IL-12/23 or IL-23 drug. An exception was made for patients who had received a minimum amount of ustekinumab at the approved dose and who had both met the required washout criterion and shown no failure of or intolerance to ustekinumab. It remains unclear whether the observed effects can be transferred to the corresponding patients.

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

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

I 7 References for English extract

Please see full dossier assessment for full reference list.

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

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