Guselkumab (Crohn's disease)

Addendum to Project A25-75 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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Table of contents

Page

List of tables v
List of abbreviations vi
1 Background 1
2 Assessment 2
2.1 Research question 1: patients who are not eligible for conventional therapy 4
2.1.1 Results on added benefit 4
2.1.1.1 Outcomes included 4
2.1.1.2 Risk of bias and certainty of conclusions 4
2.1.1.3 Results 6
2.1.2 Probability and extent of added benefit 8
2.1.2.1 Assessment of added benefit at outcome level 8
2.1.2.2 Overall conclusion on added benefit 10
2.2 Research question 2: patients who are not eligible for a biologic agent 11
2.2.1 Results on added benefit 11
2.2.1.1 Outcomes included 11
2.2.1.2 Risk of bias and certainty of conclusions 11
2.2.1.3 Results 11
2.2.2 Probability and extent of added benefit 13
2.2.2.1 Assessment of added benefit at outcome level 13
2.2.2.2 Overall conclusion on added benefit 17
2.3 Summary 17
3 References 19

List of tables

Page

Table 1: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: guselkumab versus ustekinumab 5
Table 2: Results (morbidity) – RCT, direct comparison: guselkumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) 7
Table 3: Extent of added benefit at outcome level: guselkumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy) 8
Table 4: Positive and negative effects from the assessment of guselkumab in comparison with ustekinumab (research question 1: patients who are not eligible for conventional therapy) 10
Table 5: Results (morbidity) – RCT, direct comparison: guselkumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) 12
Table 6: Extent of added benefit at outcome level: guselkumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent) 15
Table 7: 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) 17
Table 8: Guselkumab – probability and extent of added benefit 18

List of abbreviations

Abbreviation	Meaning
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)
NRI	non-responder imputation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO	patient-reported outcomes
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
TNF	tumour necrosis factor
WPAI-CD	Work Productivity and Activity Impairment Questionnaire – Crohn's Disease

1 Background

On 7 October 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-75 (Guselkumab – Benefit assessment according to § 35a Social Code Book V) [1].

In the commenting procedure Johnson & Johnson, #76}, the pharmaceutical company (hereinafter referred to as "the company") presented supplementary data that go beyond the information in the dossier [2]. The commission comprises the assessment of the following analyses presented by the company in the commenting procedure, taking into account the information provided in the dossier:

- Work Productivity and Activity Impairment Questionnaire – Crohn's Disease (WPAI-CD) item 6
- Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) with threshold value ≥ 1
- 90-day corticosteroid-free status + sustained remission (recorded using patient-reported outcome 2 (PRO2)
- Relevant subgroups and sensitivity analyses

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

2 Assessment

The double-blind, randomized controlled trial (RCT) GALAXI 1 was used to assess the benefit of guselkumab in adult patients with moderately to severely active Crohn's disease [3-6] as well as the pooled data from the RCTs GALAXI 2 [4-7] and GALAXI 3 [4-6,8], hereinafter referred to as GALAXI 2/3. Each of the RCTs compared guselkumab with ustekinumab. A detailed description of the GALAXI studies can be found in dossier assessment A25-75 [1].

Information and analyses subsequently submitted by the company

Outcome symptoms (PGIC and PGIS)

For the outcome symptoms, recorded using the PGIC and PGIS, responder analyses on improvement by ≥ 1 point were used for the benefit assessment. However, for the studies GALAXI 2 and GALAXI 3 no responder analyses on an improvement by ≥ 1 point were predefined and conducted. Consequently, no analyses for the benefit assessment were available for this operationalization for GALAXI 2/3. As part of the commenting procedure, the company had subsequently submitted the missing analyses on the improvement by ≥ 1 point for GALAXI 2/3, as well as the corresponding meta-analyses of the GALAXI studies, so that these could be used for the benefit assessment.

Activity impairment (WPAI-CD Item 6)

On a scale from 0 to 10, item 6 of the WPAI-CD measures the impairment of the daily activities (outside of work) that have occurred over the past 7 days due to Crohn's disease [9]. The impairment of activity, as recorded using WPAI-CD Item 6, was included in dossier assessment A25-75 as a relevant outcome. As described in the dossier assessment, Modules 4A and 4B of the dossier provided no data for the relevant sub-populations. The responder analyses at Week 48 (improvement by ≥ 15% of the scale range), which were submitted separately for the subpopulations along with the comments, may be used for the benefit assessment.

Outcome remission: 90 days without corticosteroids + sustained remission (PRO2)

In its dossier, the company presented various operationalizations for the outcome remission. The operationalization of corticosteroid-free remission (PRO2), defined as a stool frequency of ≤ 3 and abdominal pain of ≤ 1 at Week 48 (each recorded using the Crohn's Disease Activity Index [CDAI]) whilst remaining corticosteroid-free for a period of at least 90 days prior to Week 48, was included in the benefit assessment as being relevant to patients.

As part of the commenting procedure, the company presented analyses for a further operationalization of remission, defined as 90 days without corticosteroids plus sustained remission (PRO2). This operationalization combines sustained remission (remission in ≥ 80% of all surveys between Weeks 12 and 48, corresponding to at least 8 out of 10 surveys, always

including remission at Week 48) with corticosteroid-free status for at least 90 days prior to Week 48.

For the benefit assessment, it is usually of interest whether a patient is in remission at a relevant point in time. This point in time corresponds at least to the minimum study duration, which is 24 weeks in this therapeutic indication. This does not necessarily rule out the consideration of a symptom-free period. However, in the operationalization 90 days without corticosteroids + sustained remission (PRO2), subsequently submitted by the company with its comments, a period beginning as early as in Week 12 (Week 12 to Week 48) was used to assess sustained remission (PRO2). This does not appear appropriate, as it cannot be ruled out that patients may still achieve remission even after Week 12 or Week 20 (provided that the two symptomatic visits covered by the 80% rule defined by the company [see above] at the start of the period under consideration are taken into account). This can also be learned from the data presented by the company, which show that even after Week 12, a significant proportion of patients in the total populations of the GALAXI studies have achieved symptomatic remission. Furthermore, it is unclear why, in the operationalization subsequently submitted by the company, remission was to be achieved in only 8 out of 10 visits (80%) between Weeks 12 and 48 (always including remission at Week 48), and nothing suggests that this requirement is related to the choice of the early point in time (Week 12). In principle, this definition would mean, for example, that in addition to patients who show no symptoms at any of the visits, patients who were symptomatic at individual visits or even at two consecutive visits – and thus over a relevant period of up to 12 weeks – would also be classified as being in remission for the outcome. The operationalization 90-day corticosteroid-free status + sustained remission (PRO2) subsequently submitted by the company was therefore not used for the benefit assessment. With corticosteroid-free remission (PRO2), the company presented analyses in its dossier on a suitable operationalization for the patient-relevant outcome remission, which was included in the benefit assessment. These analyses are still considered relevant.

Subgroup analyses

Dossier assessment A25-75 [1] explains that the impact of incompletely observed patients or values imputed using non-responder imputation (NRI) on subgroup effects and interaction tests cannot be estimated. In its comments, the company does not provide any new information that would refute the criticism set out in dossier assessment A25-75. It remains unclear how the high proportions of incompletely observed patients and values imputed by means of NRI are distributed within the subgroups. In line with the outcomes already considered in dossier assessment A25-75, the subgroup analyses for the analyses subsequently submitted with the comments cannot be used for the benefit assessment either.

Sensitivity analyses

With its comments, the company now also presents the result of a meta-analysis based on the stratified study results using the inverse-variance method for the outcomes with statistically significant results from a meta-analysis using the Mantel-Haenszel method. Consequently, such results are available only for some of the outcomes considered in research question 2. The results of the meta-analysis are therefore presented across all research questions and outcomes using the Mantel-Haenszel method.

The analyses subsequently submitted by the company in the commenting procedure, which are used to derive the added benefit (WPAI-CD Item 6, PGIC and PGIS), are presented below, separately by research questions 1 and 2 of the benefit assessment. As commissioned, the results of the newly presented operationalization 90 day corticosteroid-free status + sustained remission (PRO2) are presented in Appendix A.

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

2.1.1 Results on added benefit

2.1.1.1 Outcomes included

The outcomes used for the benefit assessment are described in dossier assessment A25-75 [1].

2.1.1.2 Risk of bias and certainty of conclusions

In dossier assessment A25-75 [1], the risk of bias across outcomes was rated as low.

Table 1 shows the risk of bias for GALAXI 1 and GALAXI 2/3 at outcome level.

Table 1: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: guselkumab versus ustekinumab

Study		Outcomes												
	Study level	All-cause mortality[a]	Corticosteroid-free clinical 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	L[c]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[c]	L[e]	H[c]	–
GALAXI 2/3	L	L[c]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[d]	H[c]	L[e]	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—or the varying proportion across the arms—of values replaced by NRI.
e. Despite the low risk of bias, the certainty of results for the outcome discontinuation due to AEs was assumed to be restricted (dossier assessment A25-75, Section I 4.2.2).

AE: adverse event; H: high; IBDQ: Inflammatory Bowel Disease Questionnaire; L: low; NRI: non-responder imputation; 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

The risk of bias of the results subsequently submitted for the outcomes symptoms (PGIC and PGIS) and activity impairment (WPAI CD item 6) is rated as high in each case due to the high proportion—or the varying proportion across the arms—of values imputed by NRI. For all other outcomes, the company's comments do not provide any new information that would alter the assessment of the risk of bias described in dossier assessment A25-75. Hence, the risk of bias is still rated as high for these outcomes.

Dossier assessment A25-75 described uncertainties arising from dosing regimens for guselkumab and ustekinumab that did not fully comply with the Summary of Product Characteristics (SmPC); these were considered when assessing the certainty of conclusions of the results from GALAXI 1 and GALAXI 2/3 (see Sections I 3.2 and I 4.2.2 of the dossier assessment). This resulted in a limited certainty of conclusions both when considering the results at the level of individual studies and in the results of the meta-analysis; therefore at most hints, for example of an added benefit, were possible.

Based on the findings gained in the commenting procedure and the oral hearing, the deviation in the dosing of guselkumab and ustekinumab in the GALAXI studies is considered to be less serious than was concluded in the original dossier assessment. Consequently, based on the GALAXI studies, when considering the individual studies, at most a hint (high risk of bias or limited certainty of results for all outcomes), and when summarizing the results in a meta-analysis, at most an indication, e.g. of an added benefit, could be derived.

2.1.1.3 Results

Table 2 summarizes the subsequently submitted results on 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.

Table 2: Results (morbidity) – RCT, direct comparison: guselkumab vs. ustekinumab (research question 1: patients who are not eligible for conventional therapy)

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]
Morbidity (at Week 48)					
Symptoms – Improvement					
PGIC[b]					
GALAXI 1	29	25 (86.2)	26	24 (92.3)	0.93 [0.78; 1.12]; 0.464
GALAXI 2/3	140	120 (85.7)	140	116 (82.9)	1.04 [0.94; 1.15]; 0.471
Total[c]					1.02 [0.93; 1.11]; 0.721
PGIS[d]					
GALAXI 1	29	18 (62.1)	26	15 (57.7)	1.08 [0.71; 1.66]; 0.718
GALAXI 2/3	140	92 (65.7)	140	94 (67.1)	0.98 [0.83; 1.16]; 0.809
Total[c]					0.99 [0.85; 1.16]; 0.927
Activity impairment (WPAI-CD item 6)[e]					
GALAXI 1	29	19 (65.5)	26	18 (69.2)	0.95 [0.66; 1.37]; 0.790
GALAXI 2/3	140	85 (60.7)	140	91 (65.0)	0.94 [0.79; 1.12]; 0.481
Total[c]					0.94 [0.80; 1.10]; 0.426

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).
- Missing values were imputed using NRI.

b. Defined as any improvement ("very much improved", "much improved" or "slightly improved") from baseline.

c. 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.

d. Defined as any improvement in symptom severity on a five-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe") compared to baseline.

e. A score decrease by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 0 to 10).

CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NRI: non-responder imputation; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; RR: relative risk; WPAI-CD: Work Productivity and Activity Impairment Questionnaire for Crohn's Disease

Based on the available information, at most indications, e.g. of an added benefit, can be determined for all outcomes subsequently submitted with the comments (see Section 2.1.1.2 of this addendum for reasoning).

Morbidity

The analyses subsequently submitted by the company for the outcomes symptoms (PGIC and PGIS) and activity impairment (WPAI-CD Item 6) show no statistically significant difference between the treatment groups in either case. There was no hint of an added benefit of guselkumab over ustekinumab; an added benefit is therefore not proven.

2.1.2 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* [10].

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

2.1.2.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.1.1 and the results of dossier assessment A25-75 [1] (see Table 3).

Table 3: 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 3: 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)	85.7–86.2 vs. 82.9–92.3[c] RR: 1.02 [0.93; 1.11]; p = 0.721	Lesser benefit/added benefit not proven
Symptoms (PGIS - improvement at Week 48)	62.1–65.7 vs. 57.7–67.1[c] RR: 0.99 [0.85; 1.16]; p = 0.927	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 - improvement at Week 48)	60.7–65.5 vs. 65.0 vs. 69.2[c] 0.94 [0.80; 1.10]; p = 0.426	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)[d]	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[d]	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 3: 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 there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. Minimum and maximum proportions of events in each treatment arm in the studies included. d. Suitable data only available in GALAXI 2/3; for justification see Section I 4.2.1 of dossier assessment A25-75 [1]. 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		

2.1.2.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 4: 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**
–	–

Taking into account the analyses subsequently submitted in the commenting procedure and the results used in dossier assessment A25-75, there are neither positive nor negative effects of guselkumab compared with ustekinumab in the subpopulation relevant for research question 1.

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.

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

2.2.1 Results on added benefit

2.2.1.1 Outcomes included

The outcomes used for the benefit assessment are described in benefit assessment A25-75 [1].

2.2.1.2 Risk of bias and certainty of conclusions

The aspects relating to the risk of bias and the certainty of conclusions do not differ between research question 1 and research question 2 and are described in Section 2.1.1.2 of this addendum.

2.2.1.3 Results

Table 5 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 (tumour necrosis factor [TNF]α antagonist or integrin inhibitor or interleukin inhibitor).

Table 5: Results (morbidity) – RCT, direct comparison: guselkumab vs. ustekinumab (research question 2: patients who are not eligible for a biologic agent)

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]
Morbidity (at Week 48)					
Symptoms – Improvement					
PGIC[b]					
GALAXI 1	32	24 (75.0)	37	23 (62.2)	1.21 [0.88; 1.67]; 0.245
GALAXI 2/3	157	120 (76.4)	160	101 (63.1)	1.21 [1.04; 1.40]; 0.013
Total[c]					1.21 [1.06; 1.38]; 0.005
PGIS[d]					
GALAXI 1	32	20 (62.5)	37	18 (48.6)	1.28 [0.84; 1.97]; 0.251
GALAXI 2/3	157	101 (64.3)	160	73 (45.6)	1.40 [1.13; 1.72]; 0.002
Total[c]					1.39 [1.15; 1.67]; 0.001
Activity impairment (WPAI-CD item 6)[e]					
GALAXI 1	32	22 (68.8)	37	20 (54.1)	1.27 [0.87; 1.86]; 0.214
GALAXI 2/3	157	96 (61.1)	160	83 (51.9)	1.17 [0.97; 1.43]; 0.107
Total[c]					1.20 [1.01; 1.42]; 0.043

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).
- Missing values were imputed using NRI.

b. Defined as any improvement ("very much improved", "much improved" or "slightly improved") from baseline.

c. 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.

d. Defined as any improvement in symptom severity on a five-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe") compared to baseline.

e. A score decrease by ≥ 15% of the scale range from baseline is considered a clinically relevant improvement (scale range: 0 to 10).

CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NRI: non-responder imputation; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; RR: relative risk; WPAI-CD: Work Productivity and Activity Impairment Questionnaire for Crohn's Disease

Based on the available information, at most indications, e.g. of an added benefit, can be determined for all outcomes subsequently submitted with the comments (see Section 2.1.1.2 of this addendum for reasoning).

Morbidity

Symptoms (PGIC)

A statistically significant difference between the treatment groups in favour of guselkumab was found for the outcome symptoms (recorded using PGIC). 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.

Symptoms (PGIS)

A statistically significant difference between the treatment groups in favour of guselkumab was found for the outcome symptoms (recorded using PGIS). There is an indication of minor added benefit of guselkumab in comparison with ustekinumab.

Activity impairment (WPAI-CD Item 6)

A statistically significant difference between the treatment groups in favour of guselkumab was found for the outcome activity impairment (surveyed using the WPAI-CD Item 6). 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.

2.2.2 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* [10].

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

2.2.2.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.2.1 and the results of dossier assessment A25-75 [1] (see Table 6).

Determination of the outcome category for symptom outcomes

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

Symptoms (PGIC)

For the outcome symptoms (recorded using the PGIC), insufficient data are available which would allow a classification as severe/serious. Therefore, the outcome symptoms (PGIC) was assigned to the outcome category of non-serious/non-severe symptoms.

Symptoms (PGIS)

For the outcome symptoms (recorded using the PGIS), it is assumed that an improvement will be observed over the course of the study. At the start of the study, patients in the sub-populations from GALAXI 1 and GALAXI 2/3 relevant to research question 2 had an average score of 3.6, placing them on average between the response categories 'moderate' and 'severe'. There are no further data on the assignment to the severity category. Therefore, the outcome symptoms (PGIC) was assigned to the outcome category of non-serious/non-severe symptoms.

Activity impairment (WPAI-CD Item 6)

For the outcome activity impairment (WPAI-CD Item 6), it is assumed that an improvement will be observed over the course of the study. At the start of the study, patients in the sub-populations from GALAXI 1 and GALAXI 2/3 relevant to research question 2 had an average WPAI score of 52% to 56%, placing them on average in the middle of the range from 0% to 100%. The company did not provide any further information on the threshold value for a classification as severe/serious. Therefore, the outcome activity impairment (WPAI-CD item 6) was assigned to the outcome category non-serious/non-severe symptoms/late complications.

Table 6: 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	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ 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)	75.0–76.4 vs. 62.2–63.1[c] RR: 1.21 [1.06; 1.38]; RR: 0.83 [0.72; 0.94][d]; p = 0.005	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Symptoms (PGIS - improvement at Week 48)	62.5–64.3 vs. 45.6–48.6[c] RR: 1.39 [1.15; 1.67]; RR: 0.72 [0.60; 0.87][d]; p = 0.001 probability: indication	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
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 - improvement at Week 48)	61.1–68.8 vs. 51.9–54.1[c] RR: 1.20 [1.01; 1.42]; RR: 0.83 [0.70; 0.99][d]; p = 0.043	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]

Table 6: 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: indication	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[f]	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 there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. 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 2/3; for justification see Section I 4.2.1 of dossier assessment A25-75 [1].

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

2.2.2.2 Overall conclusion on added benefit

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

Table 7: 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
Non serious/non-severe symptoms ▪ symptoms (PGIS): indication of an added benefit – extent: "minor" health-related quality of life ▪ IBDQ total score: indication of added benefit – extent: "minor"	–
IBDQ: Inflammatory Bowel Disease Questionnaire; PGIS: Patient Global Impression of Severity	

Taking into account the analyses subsequently submitted in the commenting procedure and the results used in dossier assessment A25-75, there are positive effects of guselkumab compared with ustekinumab in the relevant subpopulation of research question 2. In the outcome category morbidity, there is an indication of a minor added benefit for the outcome symptoms (PGIS). In the outcome category health-related quality of life as well, there is an indication of minor added benefit for the total score of the Inflammatory Bowel Disease Questionnaire (IBDQ).

In summary, there is an indication 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).

2.3 Summary

The data subsequently submitted by the company in the commenting procedure and the information provided at the oral hearing change the conclusion on the added benefit of guselkumab from dossier assessment A25-75 for research question 2. Whilst in dossier assessment A25-75, there was a hint of minor added benefit due to the positive effect in health-related quality of life (IBDQ total score), this addendum reveals an indication of minor added benefit due to the positive effects on symptoms (PGIS) and health-related quality of life (IBDQ total score)

For the research question 1, there is no change in comparison with dossier assessment A25-75.

The following Table 8 shows the result of the benefit assessment of guselkumab under consideration of dossier assessment A25-75 and the present addendum.

Table 8: Guselkumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit[b]
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[c, d]	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[c, d]	Indication 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. 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.
c. 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.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

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

The G-BA decides on the added benefit.

3 References

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

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