Upadacitinib (giant cell arteritis)

Addendum to Project A25-66 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
CRP	C-reactive protein
DGRh	Deutsche Gesellschaft für Rheumatologie und Klinische Immunologie (German Society for Rheumatology and Clinical Immunology)
ESR	erythrocyte sedimentation rate
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GC	glucocorticoids
GCA	giant cell arteritis
IL	Interleukin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JAK	Janus-associated kinase
MCS	Mental Component Summary
NRI-MI	non-responder imputation/multiple imputation
PCS	Physical Component Summary
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 23 September 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-66 (Upadacitinib – Benefit assessment according to § 35a Social Code Book V) [1].

In its comments and following the oral hearing, the pharmaceutical company (hereinafter referred to as "the company") presents analyses on the SELECT-GCA study for research question 1 (adults who are candidates for therapy with glucocorticoids (GCs) alone) [2] AbbVie Deutschland, #25}, which go beyond the information provided in the dossier [3]. The commission comprises the assessment of the following data taking into account the information in the dossier:

- all subsequently submitted analyses on patient-reported outcomes
- the various analyses and operationalizations on the outcome remission. The operationalizations, which include inflammatory markers as a subcomponent, should also be taken into account and analysed.

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

For the benefit assessment A25-66 [1] of upadacitinib compared to appropriate comparator therapy in adult patients with giant cell arteritis (GCA) who are eligible for monotherapy with corticosteroids (research question 1 of the benefit assessment), a subpopulation of the double-blind, randomized controlled trial (RCT) SELECT-GCA [4-7]. The subpopulation only represents patients with new-onset GCA. A detailed description of the SELECT-GCA study and of the subpopulation used can be found in dossier assessment A25-66 [1].

The company's dossier provides not suitable data for the outcome remission and for the patient-reported outcomes [1,3]. The data subsequently submitted by the company on the outcome remission and on the patient-reported outcomes from the SELECT-GCA study are assessed below, taking into account the information in the dossier.

2.1 Assessment of the data subsequently submitted on the outcome remission

2.1.1 Background and operationalizations presented

As described in benefit assessment A25-66 [1], the SELECT-GCA study did not provide a suitable operationalization for recording the outcome remission. All analyses on the outcome remission presented by the company in the dossier can therefore not be used for the benefit assessment. The benefit assessment stated that, in order to address the reduction in GC requirements, a suitable operationalization on the remission in the present therapeutic indication should record the symptoms and also take into account a steroid threshold value or steroid-free status. The level of the selected steroid threshold should be justified, and the threshold, based on the specified dose reduction schedule, should generally be below the threshold for almost all patients from the selected point in time. Steroid reductions (below a relevant threshold value) should, if possible, be undercut for a relevant period of time and not just at a single point in time.

In its comments, the company presented four further operationalizations on remission (see Table 1).

Table 1: Operationalizations presented by the company in the comments on the outcome remission and the individual components considered therein

	Steroid-free remission	**Steroid-free complete remission**	**Sustained remission with GCs ≤ 5mg/day**	**Sustained complete remission with GCs ≤ 5mg/day**
Date of analysis	At Week 52	At Week 52	From Week 36 to Week 52	From Week 36 to Week 52
Symptoms	Absence of signs and symptoms of GCA			
Compliance with the GC tapering schedule	No criterion			
GC dose	0 mg/day	0 mg/day	≤ 5 mg/day	≤ 5 mg/day
Laboratory parameters	–	Normalization of ESR (< 30 mm/h)[a], normalization of CRP (< 1 mg/dL)	-	Normalization of ESR (< 30 mm/h)[a], normalization of CRP (< 1 mg/dL) and no increase to ≥ 1 mg/dL on 2 consecutive visits
b. The criterion may also be met if values ≥ 30 mm/h are not caused by GCA. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GC: glucocorticoids; GCA: giant cell arteritis				

The two operationalizations on steroid-free remission presented in the SELECT-GCA study were used for recording the absence of signs and symptoms of GCA while off steroids at Week 52, i.e. at a point in time without (steroid-free remission) and with consideration of the laboratory parameters erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (steroid-free complete remission).

The presented further operationalizations on sustained remission with GCs ≤ 5 mg/day were used to record the absence of GCA signs and symptoms with a simultaneous GC dose ≤ 5 mg/day from Week 36 to Week 52, i.e. over a 16-week period, each not taking into account (sustained remission with GCs ≤ 5 mg/day) and taking into account the laboratory parameters ESR and CRP (sustained complete remission with GCs ≤ 5 mg/day).

The operationalizations on the outcome remission, which include the normalization of ESR and CRP, are not suitable for the benefit assessment. The reasons for this are provided below.

An elevation of the listed laboratory parameters is not necessarily associated with noticeable symptoms for the patient. Likewise, as already described in dossier assessment A25-66, symptomatic GCA recurrence is not necessarily associated with an elevation in CRP or ESR levels [8,9]. Furthermore, acute-phase proteins such as CRP may react independently of clinical improvement when antibodies against interleukin (IL)-6 receptors, Janus-associated kinase (JAK) inhibitors or tumour necrosis factor (TNF) inhibitors are used [10-13]. If normalization of CRP levels is included in the outcome definition of remission, remission can potentially be achieved more easily in the intervention arm than in the comparator arm due

to a possible reduction in CRP levels caused by upadacitinib. A systematic review of clinical studies on rheumatoid arthritis showed that when comparing IL-6 receptor antagonists and, to a minor extent, JAK inhibitors with therapies with other mechanisms of action, outcomes that include CRP or ESR laboratory values in addition to the determination of clinical disease activity are associated with systematic overestimation of effect sizes in favour of IL-6 receptor antagonists or JAK inhibitors [14]. The considerably stronger effects observed in the SELECT-GCA study when remission was assessed taking CRP and ESR into account compared to when these were not taken into account (see Table 9 and Table 3) also point to the described overestimation of effect sizes due to the influence of JAK inhibitors on the laboratory values CRP and ESR. The statements in the comments of the company [2] and the German Society for Rheumatology and Clinical Immunology (DGRh) [15] as well as the statements made at the oral hearing [16] cannot refute the potential influence of upadacitinib on CRP levels independently of disease activity. Within the framework of the comments, the DGRh cites an observational study in patients with rheumatoid arthritis receiving the JAK inhibitor upadacitinib. The data show very similar remission rates with upadacitinib when looking at the Clinical Disease Activity Index (CDAI), which does not include CRP, compared to the Simplified Disease Activity Index (SDAI), which does include CRP [17]. This supports the potentially direct effect of upadacitinib on inflammatory markers. However, there is a lack of external control that could reveal potential differences compared to therapies without direct effects on inflammatory markers, as in Janke 2022 [14]. It is therefore still assumed that the inclusion of laboratory parameters in the definition of remission potentially leads to an unfair comparison in favour of the intervention arm. The two operationalizations presented with the company's comments on complete remission with the inclusion of CRP and ESR, are therefore not used for the benefit assessment, but are presented as supplementary information in Appendix A as requested.

The operationalization sustained remission with a GC threshold value ≤ 5 mg/day is used for the benefit assessment (see Table 1). The operationalization is based on the absence of noticeable symptoms for the patient, taking into account the GC dose. Laboratory values (ESR, CRP) are not included. The chosen GC threshold value is based on guidelines that recommend a reduction to 15 to 20 mg/day within 2 to 3 months and to ≤ 5 mg/day after 1 year [18,19]. Furthermore, sustained remission is assessed not only at a single point in time, but over a period of 16 weeks (Weeks 36 to 52), during which the threshold value used can be achieved by all patients in both study arms. The requirement that there must also have been a consistent absence of signs and symptoms of GCA during this period is assessed as a comprehensible criterion in the present context. However, it should be noted that in the SELECT-GCA study, only three recordings on symptoms (at Weeks 36, 44 and 52) were conducted during the 16-week period under review. According to the study protocol, in contrast, the steroid dose was recorded daily by means of an electronic diary over the 16-

week period. The requirement that steroid reduction should be maintained for a relevant period of time and not just at a single point in time is thus fulfilled.

The outcome operationalization of steroid-free remission at Week 52 is presented as supplementary information, as in this outcome operationalization, steroid freedom is only recorded at one point in time.

The outcome steroid freedom at Week 52, which was additionally submitted by the company in the commenting procedure, is not used for the benefit assessment, as the GC dose is already appropriately taken into account in the outcome remission.

2.1.2 Subsequently delivered analysis types and risk of bias

The company presents several analysis and imputation strategies for the handling of intercurrent events and missing values for the outcome operationalization sustained remission with GCs ≤ 5mg/day (Weeks 36 to 52) (see Table 2). The same applies to the steroid-free remission at Week 52, which is presented as supplementary information in this addendum. When taking intercurrent events into account, observed values are imputed in the manner described in Table 2. In the case of the treatment policy strategy, all observed values are included in the analysis without taking intercurrent events into account.

Table 2: Analysis and imputation strategies for sustained remission with GC ≤ 5 mg/day presented by the company in its comments (Weeks 36 to 52)

Treatment Policy strategy		**Consideration of intercurrent events**	
NRI-MI[a,b]	**MI[a, b]**	**NRI-MI[a,b]**	**MI[a, b]**
Imputation of missing values using NRI	Imputation of missing values using MI	Imputation in case of premature discontinuation of the study medication and in case of missing values using NRI; imputation in case of > 100 mg prednisone or equivalent dose for an indication other than GCA using MI	Imputation in case of premature discontinuation of the study medication, in case of > 100 mg prednisone or equivalent dose for an indication other than GCA, and in case of missing values using MI

a. Missing values attributable to logistical restrictions related to COVID-19 were generally imputed with MI; there were no missing values related to COVID-19 in the submitted subpopulation.
b. If a patient was classified as a responder both before and after the visit, he or she will also be rated as a responder for the missing visit. It is unclear how many patients this affects and whether this imputation applies only to NRI-MI or also to MI.

GCA: giant cell arteritis; MI: multiple imputation; NRI: non-responder imputation; NRI-MI: non-responder imputation/multiple imputation

When comparing the results of the analysis strategies “taking intercurrent events into account” and “treatment policy”, it is noticeable that after the imputation using non-

responder imputation/multiple imputation (NRI-MI), more responders occur under the treatment policy strategy (additional responders under treatment policy NRI-MI: 4 vs. 1 patients in the intervention vs. control arm) [2]. Since upon consideration of the intercurrent events, treatment dropouts were imputed as non-responders it can be assumed that the 4 vs. 1 patients are patients who ultimately achieved remission despite premature treatment discontinuation. No information is available on subsequent therapies after treatment discontinuation. However, it is assumed that patients received GC therapy after discontinuation of treatment with upadacitinib or placebo. Since informative data were thus still recorded even after treatment discontinuation, the analysis strategy of treatment policy is used in the present assessment situation.

When looking at the results of the treatment policy strategy with MI, the higher proportion of patients additionally imputed as responders compared to NRI-MI is striking (additional responders under MI vs. NRI-MI: 9 vs. 7 patients in the intervention vs. control arm) [2]. These patients are those who discontinued the study and were imputed as responders. However, since both study and treatment dropouts received treatment of physician's choice or therapy with GCs (in the case of study discontinuation outside of the study), the proportion of missing values imputed as responders with the help of MI appears too high compared to the proportion of responders who remained in the study after treatment discontinuation (n = 4 vs. 1, see above). Therefore, in this data situation, imputation using NRI-MI is applied.

Imputation of missing values using NRI-MI is subject to uncertainty, e.g. because patients who discontinued the study may also be responders. Furthermore, it remains unclear how many patients were imputed as responders if they were rated as responders both before and after a missed visit. The risk of bias for the outcome remission, operationalized as sustained remission with GC ≤ 5 mg/day (Weeks 36 to 52), is therefore rated as high.

2.1.3 Results

Table 3 summarizes the results on the comparison of upadacitinib + GCs with placebo + GCs in patients with new-onset active GCA for the outcome remission.

Table 3: Results (morbidity) – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs

Study outcome category outcome	Upadacitinib + GCs		Placebo + GCs		Upadacitinib + GCs vs. placebo + GCs
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
SELECT-GCA					
Morbidity					
Remission[a]					
Sustained remission mit GC dose ≤ 5 mg/day (Weeks 36–52)[b]	148	83 (56.1)	76	28 (36.8)	1.50 [1.08; 2.07]; 0.014[c]
Steroid-free remission at Week 52[d] (supplementary information)	*148*	*87 (58.8)*	*76*	*28 (36.8)*	*1.57 [1.14; 2.15]; 0.006[c]*

a. Intercurrent events were not considered in the analysis (treatment policy); missing values were imputed using NRI-MI.
b. Defined as (number and percentage in the intervention vs. control arm per component in brackets): absence of signs and symptoms of GCA (98 [66.2%] vs. 39 [51.3%]) and GC dose ≤ 5mg/day (92 [62.2%] vs. 34 (44.7%)), each in the period from Week 36 to Week 52.
c. RR stratified by GC dose at baseline (prednisone or prednisolone > 30 mg/≤ 30 mg); calculation of 95% CI and p-value using normal distribution approximation.
d. Defined as (number and percentage in the intervention vs. control arm per component in brackets): absence of signs and symptoms of GCA (118 [79.7%] vs. 55 [72.4%]) and steroid-free status (90 [60.8%] vs. 30 [39.5%]), each at Week 52; deviations between the data in Module 4 G of the dossier and the comments regarding the absence of signs and symptoms of GCA; the values from the comments were used.

CI: confidence interval; GCA: giant cell arteritis; GCs: glucocorticoids; n: number of patients with (at least one) event; N: number of analysed patients; NRI-MI: non-responder imputation/multiple imputation; RCT: randomized controlled trial; RR: relative risk

As described in dossier assessment A25-66, due to uncertainty as to whether all patients in the subpopulation of the SELECT-GCA study presented by the company are candidates for therapy with GCs alone, at most hints, e.g. of added benefit, can be determined for the results on all outcomes.

Morbidity

Sustained remission with GCs ≤ 5mg/day (Weeks 36 to 52)

For the outcome remission, operationalized as sustained remission with GC ≤ 5 mg/day (Weeks 36 to 52), there was a statistically significant difference in favour of upadacitinib + GCs compared with placebo + GCs. However, the extent of the effect was no more than marginal (see Section 2.3.1). There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

2.1.4 Subgroups

The following potential effect modifiers were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)

No relevant effect modification by the characteristics age or sex was identified for the outcome remission operationalized as sustained remission with GCs ≤ 5mg/day (Weeks 36 to 52).

2.2 Assessment of the data subsequently submitted on patient-reported outcomes

2.2.1 Background and operationalizations presented

As described in benefit assessment A25-66 [1], the company's dossier provided no suitable data for all patient-reported outcomes used, i.e. fatigue (recorded using the Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue), health status (recorded using the EQ-5D VAS), pain (recorded using the Patient Global Impression of Change [PGIC]) and health-related quality of life (recorded with the SF-36). This was due to the potentially high proportion of imputations of patients who were classified as non-responders solely on the basis of the initiation of rescue therapy, as well as the varying proportion of patients who initiated rescue therapy in the study arms. Furthermore, only limited information was available on the missing and imputed values and on the reasons for the imputations for the subpopulation presented by the company. In its comments and following the oral hearing, the company submits further analyses that address or take into account the points of criticism from the benefit assessment (see Section 2.2.3).

Furthermore, the company's dossier only contained analyses on improvement for the patient-reported outcomes (at Week 52). However, as described in dossier assessment A25-66, the sole consideration of analyses on improvement is not adequate in the present therapeutic indication, as both improvement and deterioration are possible and relevant for patients. In its comments and following the oral hearing, the company also presented analyses on deterioration at Week 52 for the patient-reported outcomes.

The baseline values basically allow for development in both directions for the subpopulation under consideration. The values of the scales considered are partly in the upper positive range (e.g. FACIT Fatigue: 37.5 vs. 38.7 on a scale of 0 to 52) or in the middle to slightly worse range compared to the general population (SF-36 Mental Component Summary [MCS]: 48.6 vs. 51 MCS and Physical Component Summary [PCS]: 44.3 vs. 46.2; a value of 50 corresponds to the mean of the normal population), meaning that both improvement and deterioration are possible. Furthermore, the subsequently submitted data show that, with the exception of the outcome pain (PGIC), both improvements and deteriorations of a relevant extent are apparent in the outcomes used. In the present data situation and taking into account the therapeutic indication, in which patients with clinically stable disease receive additional therapy in the

intervention arm and GC tapering therapy in both study arms, the analyses of both improvement and deterioration at Week 52 are used.

2.2.2 Outcome pain (PGIC)

As described in benefit assessment A25-66 [1], the PGIC analyses on strong improvement ("very strong improvement" and "strong improvement") represent the prespecified analysis, and the analyses on any improvement represent a post-hoc analysis. Therefore, both the results for the proportion of patients who show a strong improvement and the results for the proportion of patients who show a strong deterioration, each at Week 52, should be presented.

Due to the predefinition, either strong improvement or strong deterioration was used for the benefit assessment.

In its comments, the company presented further analyses (see Section 2.2.3 below) on both any and strong improvement and deterioration. Following the oral hearing, the company presented further analyses requested by the G-BA on improvement using the treatment policy analysis strategy with MI imputation (see Section 2.2.3 below) and subgroup analyses on patient-reported outcomes. However, regarding the PGIC, the company only conducted an analysis on any improvement. For the analysis strategy “treatment policy MI” used in this addendum (see Section 2.2.3 below), there are therefore no suitable data available on strong improvement.

2.2.3 Subsequently delivered analysis types and risk of bias

The company presents several analysis and imputation strategies for the handling of intercurrent events and missing values for patient-reported outcomes (see Table 4).

Table 4: Analysis and imputation strategies for patient-reported outcomes presented by the company in its comments

Treatment policy[a]		**Consideration of intercurrent events[b]**	
NRI-MI[c]	**MI[c]**	**NRI-MI[c]**	**MI[c]**
Imputation of missing values using NRI	Imputation of missing values using MI	Imputation with increased GC dose due to rescue therapy at Week 52 and with missing values using NRI	Imputation with increased GC dose due to rescue therapy at Week 52 and with missing values using MI

a. Presented for improvement and deterioration.
b. Presented for improvement.
c. Missing values attributable to logistical restrictions related to COVID-19 were generally imputed with MI; there were no missing values related to COVID-19 in the submitted subpopulation.

GCs: glucocorticoids; MI: multiple imputation; NRI: non-responder imputation; NRI-MI: non-responder imputation/multiple imputation

The analysis strategy, which takes into account intercurrent events, was presented by the company solely for the purpose of improving patient-reported outcomes. This analysis strategy, in which patients receiving increased GC doses are imputed with NRI-MI or MI at Week 52 due to a rescue therapy, is not appropriate, as an increased GC dose does not constitute an obstacle to improvement in a patient-reported outcome.

The company did not present any analyses for the deterioration using the analysis strategy "taking intercurrent events into account", as according to the company, NRI would not have been appropriate in this situation. Irrespective of this, both the improvement and deterioration in patient-reported outcomes at Week 52 are assessed using the treatment policy strategy which does not take into account the intercurrent event "use of emergency therapy" (and the associated increase in the GC dose) and thus includes all patient-reported values at Week 52 in the analysis.

The values to be imputed in the treatment policy strategy using NRI-MI or MI are derived from the missing values of study dropouts and the missing values of patients for whom it remains unclear why the questionnaire was not completed. The proportion of missing values without information on the reasons, related to all values to be imputed, ranges between 11% and 25% (3 out of 27 to 8 out of 32 patients) in the intervention arm and 23% to 29% (5 out of 22 to 7 out of 24 patients) in the comparator arm, depending on the patient-reported questionnaire. Even if the imputation of missing values of the study dropouts as non-responders seems justified, this cannot be assessed for the missing values without information on the reasons. As these proportions appear high, imputation using MI is preferred in the present data situation, as this imputation better reflects the uncertainty in the data.

However, since the imputation of the missing values using MI is still subject to uncertainty, the risk of bias in the results on all patient-reported outcomes is rated as high.

2.2.4 Results

Table 5 summarizes the results on the comparison of upadacitinib + GCs with placebo + GCs in patients with new-onset active GCA for the patient-reported outcomes. Where necessary, the data provided by the company are supplemented with calculations conducted by the Institute.

Table 5: Results (morbidity, health-related quality of life) – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs (multipage table)

Study outcome category outcome	Upadacitinib + GCs		Placebo + GCs		Upadacitinib + GCs vs. placebo + GCs
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
SELECT-GCA					
Morbidity (Week 52)					
Fatigue (FACIT-Fatigue)[a]					
Improvement[b]	148	25 (16.9)	76	8 (10.5)	1.66 [0.67; 4.14]; 0.273[c]
Deterioration[b]	148	28 (18.9)	76	15 (19.7)	0.94 [0.50; 1.79]; 0.861[c]
Health status (EQ-5D VAS)[a]					
Improvement[d]	148	38 (25.7)	76	15 (19.7)	1.32 [0.72; 2.44]; 0.370[c]
Deterioration[d]	148	15 (10.1)	76	15 (19.7)	0.54 [0.25; 1.18]; 0.124[c]
Pain (PGIC)[a]					
Strong or very strong improvement	No suitable data (see Section 2.2.2)				
Strong or very strong deterioration	148	1 (0.7)	76	1 (1.3)	0.51 [0.03; 8.10]; 0.736[e]
Health-related quality of life (Week 52)					
SF-36 (Week 52)[a, f]					
Physical Component Summary (PCS)					
Improvement[g]	148	22 (14.9)	76	9 (11.8)	1.18 [0.53; 2.67]; 0.683[c]
Deterioration[g]	148	11 (7.4)	76	7 (9.2)	0.82 [0.26; 2.62]; 0.742[c]
Mental Component Summary (MCS)					
Improvement[g]	148	21 (14.2)	76	11 (14.5)	1.00 [0.43; 2.31]; 0.996[c]
Deterioration[g]	148	22 (14.9)	76	4 (5.3)	3.02 [0.87; 10.45]; 0.081[c]

a. Intercurrent events were not considered in the analysis (treatment policy); missing values were imputed using MI.
b. An increase/decrease by ≥ 8 points (15% of the scale range) from baseline is considered a clinically relevant improvement/deterioration (score range of the scale 0 to 52).
c. RR stratified by GC dose at baseline (prednisone or prednisolone > 30 mg/≤ 30 mg); the RR result is based on 30 imputation data sets, the results of which were summarized using Rubin's rule; calculation of 95% CI and p-value using normal distribution approximation.
d. An increase/decrease by ≥ 15 points (15% of the scale range) from baseline is considered a clinically relevant improvement/deterioration (score range of the scale: 0 to 100).
c. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [20]).
f. No information is available on the subscales for the SF-36.
g. An increase/decrease in PCS by ≥ 9.4 points or in MCS by ≥ 9.6 points from baseline is considered a clinically relevant improvement/deterioration (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 norm sample [21]).

Table 5: Results (morbidity, health-related quality of life) – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs (multipage table)

Study outcome category outcome	Upadacitinib + GCs		Placebo + GCs		Upadacitinib + GCs vs. placebo + GCs
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; GCs: glucocorticoids; MCS: Mental Component Summary; MI: multiple imputation; n: average number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; RR: relative risk; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale					

Morbidity

Fatigue (FACIT-Fatigue), health status (EQ-5D VAS)

For the outcomes fatigue, recorded using the FACIT-Fatigue, and health status, recorded using EQ-5D VAS, there were no differences between the treatment groups in terms of improvement or deterioration at Week 52. There is no hint of an added benefit of upadacitinib over GCs in each case; an added benefit is therefore not proven.

Pain (PGIC)

No suitable data are available for the outcome pain, recorded using the PGIC (see Section 2.2.2 for reasons). No differences between the treatment groups were shown for the operationalization strong deterioration. There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven. Notwithstanding this, there are no statistically significant differences between the treatment groups in terms of operationalization on any improvement or deterioration for the MI treatment policy strategy used in this addendum.

Health-related quality of life

SF-36

Health-related quality of life was recorded using the PCS and the MCS of the SF-36. For health-related quality of life measured using the SF-36, there was no difference between the treatment groups in terms of both improvement or deterioration at Week 52. There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

2.2.5 Subgroups

The following potential effect modifiers were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)

- Sex (male versus female)

No relevant effect modification by the characteristics age or sex was identified for the improvement in the patient-reported outcomes health status (EQ-5D VAS) and health-related quality of life (SF-36 [MCS and PCS]) used in this assessment. For the outcome fatigue (FACIT-Fatigue), consideration of improvement also revealed no effect modification for the characteristic sex.

For deterioration, no relevant effect modifications by the characteristic sex were observed for the outcomes fatigue (FACIT-fatigue), health status (EQ-5D VAS) and health-related quality of life (SF-36). The same applies to the outcome fatigue (FACIT-Fatigue) for the characteristic age. It should be noted that only subgroup analyses based on imputation using NRI-MI are available for the deterioration, whereas the MI imputation strategy is used for the main analysis. However, since there are no effect modifications for the mentioned outcomes and characteristics in terms of deterioration based on NRI-MI, not even those with p-values close to the significance threshold, it can be assumed in the present data situation that there are also no effect modifications with regard to age or sex for the aforementioned instruments in case of imputation with MI.

For the outcome fatigue (FACIT fatigue), the company does not specify an interaction p-value on the characteristic age for the improvement and does not present any subgroup results. The same applies to the outcomes health status (EQ-5D VAS) and health-related quality of life (SF-36 [MCS and PCS]) for the deterioration when the characteristic “age” is considered. The reason for the absence of interaction p-values is that 0% (or 100%) of events occurred in the intervention or control arm in one of the subgroups. It is therefore not possible to assess whether there is an effect modification for these outcomes and characteristics. However, with the help of a variance correction, it would still have been possible to calculate an interaction p-value. However, the company did not present corresponding analyses.

For the outcome PGIC in the operationalization “strong improvement”, assessment of the subgroup analyses is generally omitted, as the company did not provide suitable data for the main analysis (Treatment Policy MI) (see Section 2.2.2). For the PGIC, no subgroup analyses are available in the operationalization “strong deterioration”. However, due to the low number of events (intervention vs. control arm: 1 vs. 1), it can be assumed that the subgroup analyses do not have any informative value.

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [22].

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

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Sections 2.1 and 2.2 and benefit assessment A25-66 [1] (see Table 6).

Determination of the outcome category for the morbidity outcomes

Sustained remission mit GC dose ≤ 5 mg/day (Weeks 36–52)

The company assigned all outcome operationalizations for remission to the outcome category serious/severe symptoms/late complications. It justifies this classification with the severity of the disease, which, according to company, causes serious symptoms in the affected patients, accompanied by the risk of blindness, as well as serious late complications and an increased risk of mortality.

In case of GC monotherapy, the guidelines recommend a gradual reduction only in the absence of signs and symptoms of GCA [18,19]. According to the study protocol, patients had to be clinically stable at baseline (as assessed by the investigator) in order to start with the GC tapering schedule. Based on the available data, it cannot be conclusively assessed whether all patients in the SELECT-GCA study were symptom-free at baseline. Due to the gradual tapering of GC therapy in the SELECT-GCA study, it can be assumed that symptoms of the disease may recur in the form of relapses during the course of the study. In the present situation, the symptoms observed during the course of the study are therefore considered in order to assess the severity of the outcome remission operationalized as sustained remission with a GC dose ≤ 5 mg/day. No information is available for the relevant subpopulation on the symptoms at baseline and in the course of the study.

Information on symptoms for the relevant subpopulation includes only ischaemia-related loss of vision (18 [12.2%] vs. 22 [29.0%] patients). However, these figures refer to the period of eight weeks prior to study inclusion. As described above, patients had to be clinically stable at baseline and therefore suitable for GC tapering. It is therefore assumed that these symptoms no longer existed when the study started.

Information on the GCA symptoms during the course of the study is available for the total population of the SELECT-GCA study. These refer to the period between Week 2 and Week 52. Information on the start of the study is also not available for the total population. The data for the total population will be considered in more detail below. 31 of 208 (14.9%) patients in the intervention arm and 21 of 111 (18.9%) patients in the comparator arm showed at least 1 sign or symptom of GCA at Week 2. The proportion of patients with at least one sign or

symptom of ATA during the study up to week 52 was less than 20% in both groups combined. The following individual symptoms were recorded in relation to the signs or symptoms of GCA: pyrexia, symptoms of polymyalgia rheumatica, headache or tenderness of the scalp or temporal artery, visual signs or symptoms such as subacute loss of vision due to arteritic anterior ischaemic optic neuropathy or temporary blurred vision, jaw or oral pain, new-onset or worsening claudication of the extremities, and a category of other signs associated with GCA or PMR flares. Based on the available information, it is not possible to assess the severity of the symptoms reported. Only for subacute loss of vision due to arteritic anterior ischaemic optic neuropathy and potentially also for new or worsening claudication of the extremities, assuming that these are severe/serious symptoms. However, visual signs or symptoms such as subacute loss of vision due to arteritic anterior ischaemic optic neuropathy or temporary blurred vision occurred in only very few patients during the course of the study. It is also unclear in which of these patients these signs were symptoms of loss of vision. New-onset or worsening claudication of the extremities also affected very few patients over the course of the study. Based on this information on symptoms in the total population during the course of the study, no severe or serious symptoms are to be expected for the majority of patients in the subpopulation used. Overall, the SELECT-GCA study thus provides no information for the subpopulation of patients with new-onset GCA that would allow a classification as serious/severe. The outcome remission, operationalized as sustained remission with a GC dose ≤ 5 mg/day (Weeks 36 to 52), is therefore assigned to the outcome category non-serious/non-severe symptoms/late complications.

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

Outcome category **outcome**	**Upadacitinib + GCs vs. placebo + GCs** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	1.4 vs. 2.6 RR: 0.51 [0.07; 3.57]; p = 0.597	Lesser benefit/added benefit not proven
Morbidity		
Remission		
Sustained remission with GC dose ≤ 5mg/day (Weeks 36 to 52)	56.1 vs. 36.8 RR: 1.50 [1.08; 2.07]; RR: 0.67 [0.48; 0.93][c]; p = 0.014	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[d]
Fatigue (FACIT-Fatigue)		
Improvement by ≥ 8 points	16.9 vs. 10.5 RR: 1.66 [0.67; 4.14]; p = 0.273	Lesser benefit/added benefit not proven
Deterioration by ≥ 8 points	18.9 vs. 19.7 RR: 0.94 [0.50; 1.79]; p = 0.861	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)		
Improvement by ≥ 15 points	25.7 vs. 19.7 RR: 1.32 [0.72; 2.44]; p = 0.370	Lesser benefit/added benefit not proven
Deterioration by ≥ 15 points	10.1 vs. 19.7 RR: 0.54 [0.25; 1.18]; p = 0.124	Lesser benefit/added benefit not proven
Symptoms (PGIC)		
Strong or very strong improvement	No suitable data[e]	Lesser benefit/added benefit not proven
Strong or very strong deterioration	0.7 vs. 1.3 RR: 0.51 [0.03; 8.10]; p = 0.736	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36 (PCS)		
Improvement by ≥ 9.4 points	14.9 vs. 11.8 RR: 1.18 [0.53; 2.67]; p = 0.683	Lesser benefit/added benefit not proven

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

Outcome category **outcome**	**Upadacitinib + GCs vs. placebo + GCs** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Deterioration by ≥ 9.4 points	7.4 vs. 9.2 RR: 0.82 [0.26; 2.62]; p = 0.742	Lesser benefit/added benefit not proven
SF-36 (MCS)		
Improvement by ≥ 9.6 points	14.2 vs. 14.5 RR: 1.00 [0.43; 2.31]; p = 0.996	Lesser benefit/added benefit not proven
Deterioration by ≥ 9.6 points	14.9 vs. 5.3 RR: 3.02 [0.87; 10.45]; p = 0.081	Lesser benefit/added benefit not proven
Side effects		
SAEs	24.3 vs. 25.0 RR: 0.97 [0.60; 1.58]; p = 0.923	Greater/lesser harm not proven
Severe AEs	34.5 vs. 30.3 RR: 1.14 [0.76; 1.71]; p = 0.615	Greater/lesser harm not proven
Discontinuation due to AEs	17.6 vs. 25.0 RR: 0.70 [0.42; 1.19]; p = 0.194	Greater/lesser harm not proven
Infections (AEs)	64.9 vs. 55.3 RR: 1.17 [0.93; 1.48]; p = 0.172	Greater/lesser harm not proven
Serious infections (SAEs)	6.1 vs. 10.5 RR: 0.58 [0.23; 1.44]; p = 0.309	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
e. See Section 2.2.2 of this addendum for the reasoning.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; PGIC: Patient Global Impression of Change; RR: relative risk; SAE: serious adverse event; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale

2.3.2 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 upadacitinib in comparison with GCs

Positive effects	Negative effects
–	–
GCs: glucocorticoids	

Based on the subpopulation of the SELECT-GCA study relevant to research question 1, there were neither positive nor negative effects from the assessment of upadacitinib compared to the ACT.

In summary, for patients with GCA who are candidates for therapy with GCs alone (research question 1), there is no hint of an added benefit of upadacitinib over the ACT systemic GCs; an added benefit is therefore not proven.

2.4 Summary

The data subsequently submitted by the company for research question 1 in the commenting procedure do not change the conclusion on the added benefit of upadacitinib drawn in dossier assessment A25-66.

The following Table 8 shows the result of the benefit assessment of upadacitinib under consideration of dossier assessment A25-66 and the present addendum.

Table 8: Upadacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with GCA who are candidates for therapy with glucocorticoids alone	Treatment with systemic GCs	Added benefit not proven
2	Adults with GCA who are not candidates for therapy with glucocorticoids aloneb	Therapy with systemic GCs in combination with tocilizumab	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, research question 2 may include GCA patients with relapse, refractory GCA patients or patients who have not tolerated GC therapy or who are at high risk regarding GC-induced side effects.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GCA: giant cell arteritis; GCs: glucocorticoids

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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Appendix A Results on complete remission

Table 9: Results (morbidity, supplementary presentation) – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs

Study outcome category outcome	Upadacitinib + GCs		Placebo + GCs		Upadacitinib + GCs vs. placebo + GCs
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
SELECT-GCA					
Morbidity					
Remission[a]					
Sustained complete remission mit GC dose ≤ 5 mg/day (Weeks 36–52)[b]	148	69 (46.6)	76	15 (19.7)	2.32 [1.43; 3.75]; < 0.001[c]
Steroid-free complete remission (at Week 52)[d]	148	80 (54.1)	76	16 (21.1)	2.52 [1.60; 3.96]; < 0.001[c]

a. Intercurrent events were not considered in the analysis (treatment policy); missing values were imputed using NRI-MI.

b. Defined as (number and percentage in the intervention vs. control arm per component in brackets): absence of GCA signs and symptoms (98 [66.2%] vs. 39 [51.3%]), GC dose ≤ 5 mg/day [92 [62.2%]) vs. 34 [44.7%]), normalization of ESR (< 30 mm/h) (105 [70.9%] vs. 44 [57.9%]) and normalization of CRP (< 1 mg/dL) (101 [68.2%] vs. 33 [43.4%]) in the period from Week 36 to Week 52; the criterion of ESR normalization may also be met if values ≥ 30 mm/h are not caused by GCA.

c. RR stratified by GC dose at baseline (prednisone or prednisolone > 30 mg/≤ 30 mg); calculation of 95% CI and p-value using normal distribution approximation.

d. Defined as (number and percentage in the intervention vs. control arm for each component in brackets): absence of GCA signs and symptoms (118 [79.7%] vs. 55 [72.4%]), steroid freedom (90 [60.8%] vs. 30 [39.5%]), normalization of ESR (< 30 mm/h) (119 [80.4%] vs. 51 [67.1%]) and normalization of CRP (< 1 mg/dL) (118 [79.7%] vs. 41 [53.9%]) each at Week 52; the criterion of ESR normalization may also be met if values ≥ 30 mm/h are not caused by GCA; deviations between Module 4 G of the dossier and the comments regarding the absence of GCA signs and symptoms; the data in the comments were used.

CI: confidence interval; CRP: C-reactive protein; GCA: giant cell arteritis; GCs: glucocorticoids; ESR: erythrocyte sedimentation rate; n: number of patients with (at least one) event; N: number of analysed patients; NRI-MI: non-responder imputation/multiple imputation; RCT: randomized controlled trial; RR: relative risk