Upadacitinib (giant cell arteritis)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Upadacitinib (Riesenzellarteriitis) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

Patient and family involvement

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

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Part I: Benefit assessment

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I List of tables[2]

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GC	glucocorticoids
GCA	giant cell arteritis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	mental component summary
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short-Form 36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TNF	tumour necrosis factor

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug upadacitinib. 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 15 May 2025.

Research question

The aim of this report was to assess the added benefit of upadacitinib compared with the appropriate comparator therapy (ACT) in adult patients with giant cell arteritis (GCA).

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 upadacitinib

Research question	Therapeutic indication	ACT[a]
1	Adults with GCA who are candidates for therapy with glucocorticoids alone	Treatment with systemic glucocorticoids
2	Adults with GCA who are not candidates for therapy with glucocorticoids alone[b]	Treatment with systemic glucocorticoids in combination with tocilizumab

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 glucocorticoid-induced side effects.

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

The company followed the G-BA's specification of the ACT for both research questions.

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

Research question 1: Adults with GCA who are candidates for therapy with glucocorticoids (GCs) alone

Study pool and study design

The SELECT-GCA study was included in the benefit assessment.

The SELECT-GCA study is a completed, double-blind, multicentre, triple-arm RCT comparing 15 mg upadacitinib + GCs, 7.5 mg upadacitinib + GCs and placebo + GCs in adults with new-onset or recurrent active GCA. Patients had to have been treated with ≥ 40 mg prednisone (or equivalent) at any time in the past, and with ≥ 20 mg prednisone/prednisolone at the start of the study. Patients also had to have sufficient clinical stability for the GC tapering schedule specified in the study protocol as assessed by the investigator.

A total of 428 patients were included in the study and randomly allocated in a 2:1:1 ratio to the treatment arms upadacitinib 15 mg + GCs (N = 209), upadacitinib 7.5 mg + GCs (N = 107) and placebo + GCs (N = 112). Randomization was stratified according to GC dose at baseline (prednisone/prednisolone > 30 mg vs. prednisone/prednisolone ≤ 30 mg), previous treatment with an interleukin (IL)-6 inhibitor (yes vs. no) and disease status at baseline (new-onset GCA vs. recurrent GCA). At the end of the 52-week double-blind phase, patients who met the criteria for sustained remission from Week 24 or who had no symptoms or signs of GCA at Week 52 and were GC-free could participate in a blinded 52-week extension phase. The results of this extension phase are irrelevant for this benefit assessment.

The dosage of 7.5 mg upadacitinib per day is not covered by the marketing authorization. The upadacitinib 7.5 mg + GC arm is thus irrelevant for the present benefit assessment. Treatment with upadacitinib in the upadacitinib 15 mg + GC arm (hereinafter referred to as the intervention arm) followed the specifications of the Summary of Product Characteristics (SmPC). In the comparator arm, patients received an analogue therapy with placebo. In the two relevant study arms, GCs were tapered according to a predetermined schedule. A first unblinded tapering phase of varying duration up to a daily dose of 20 mg took place depending on the starting dose. Subsequently, GCs were completely tapered in a blinded regimen by Week 26 at the latest in the intervention arm and Week 52 in the comparator arm. In the event of GCA recurrence or if the patient was unable to follow the tapering schedule, tapering was interrupted and prednisone/prednisolone was administered unblinded as rescue therapy so that the daily GC dose was at least 20 mg.

The primary outcome of the study was sustained remission from Week 12 to Week 52, defined as the absence of signs or symptoms of GCA and adherence to the GC tapering schedule specified in the study protocol. Moreover, outcomes were recorded in the categories morbidity, health-related quality of life and adverse events (AEs).

Relevant subpopulation

In this therapeutic indication, the G-BA differentiates between adult patients with GCA who are candidates for systemic therapy with GCs alone (research question 1) and those who are not candidates for systemic therapy with GCs alone (research question 2). Research question 1 particularly comprises patients with new-onset GCA who tolerate GC therapy and are not at

high risk of GC-induced side effects. According to the S2k guideline of the German Society for Rheumatology and Clinical Immunology (Deutsche Gesellschaft für Rheumatologie und Klinische Immunologie [DGRh]) and the recommendations of the European League Against Rheumatism (EULAR), there is an increased risk of GC-induced or GC-aggravated side effects and complications in patients with existing infectious diseases, cardiovascular events, arterial hypertension, diabetes mellitus, osteoporosis, weight gain, glaucoma, cataracts and adrenal insufficiency.

For the assessment of research question 1, the company presented a subpopulation from the SELECT-GCA study in its dossier, which only included patients with new-onset GCA. This subpopulation comprised 148 patients in the intervention arm and 76 in the comparator arm. According to the company, this population is suitable to adequately derive the added benefit for research question 1. The company justified this with the fact that in the subpopulation presented by it, those patients were excluded who had a relapse and could therefore be assigned to research question 2 according to the G-BA's information. According to the company, patients who did not tolerate GC therapy or had existing cardiovascular diseases, arterial hypertension or infectious diseases as comorbidities were also excluded from participation in the SELECT-GCA study. However, in the subpopulation presented by the company, a total of 29% vs. 36% of patients had at least one of the other comorbidities mentioned in the guidelines that are associated with an increased risk of GC-induced side effects (osteoporosis, diabetes mellitus, cataract, glaucoma and adrenal insufficiency). The company argues that no effect modifications were found in the results of the relevant outcomes for the characteristic comorbidities (yes vs. no), and that the results of the subgroup “comorbidity - no” were consistent with the results of the subpopulation for research question 1. Therefore, the presented subpopulation could be used to derive the added benefit of research question 1.

Concurring with the company, the subpopulation presented was used for the assessment of the added benefit for research question 1. However, despite the absence of effect modifications for the characteristic comorbidities (yes vs. no), there is uncertainty as to whether all patients in the subpopulation presented by the company were candidates for therapy with GCs alone. This uncertainty was taken into account in the assessment of the certainty of conclusions.

Data cut-offs

The present benefit assessment uses the results from the 06 February 2024 data cut-off for all relevant outcomes.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for the SELECT-GCA study.

The risk of bias for the results on the outcome discontinuation due to AEs must be rated as low. There is a high risk of bias for the outcome all-cause mortality and for the other outcomes in the side effects category.

Overall, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the SELECT-GCA study.

Results

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found for the outcome overall survival. There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

Morbidity

Remission

No suitable data are available for the outcome remission, as the operationalizations presented by the company for all remission outcomes contain components that are not suitable for the benefit assessment. For example, the outcome component "adherence to the GC tapering scheme specified in the study protocol" is not assessed as an adequate component of the remission outcome as any deviation from the specified prescribed tapering scheme led to a classification as non-responder and thus constituted an exclusion criterion for achieving remission. This does not appear appropriate against the background of any necessary individualization of the GC regimen.

In addition, the operationalization on the outcomes complete remission and sustained complete remission include the laboratory parameters erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which are not necessarily associated with noticeable symptoms for the patient. There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

Fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue), health status (EQ-5D VAS) and symptoms (Patient Global Impression of Change [PGIC])

No suitable data are available for the outcomes fatigue, recorded using FACIT-Fatigue, health status, recorded using EQ-5D VAS, and symptoms, recorded using PGIC, due to potentially inadequate imputation strategies. There is no hint of an added benefit of upadacitinib over GCs in each case; an added benefit is therefore not proven.

Health-related quality of life

SF-36

Health-related quality of life was recorded using the Physical Component Summary (PCS) and the Mental Component Summary (MCS) of the Short-Form 36 Health Survey (SF-36). No suitable data are available for health-related quality of life measured using the SF-36 due to potentially inadequate imputation strategies. There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

Side effects

Serious adverse event (SAEs), severe AEs, discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the outcomes SAEs, severe AEs and discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from upadacitinib in comparison with GCs; greater or lesser harm is therefore not proven.

Infections (AEs), serious infections (SAEs)

No statistically significant differences between the treatment arms were shown for the outcomes "infections" (AEs) and "serious infections" (SAEs). In each case, there is no hint of greater or lesser harm from upadacitinib in comparison with GCs; greater or lesser harm is therefore not proven.

Research question 2: Adults with GCA who are not candidates for therapy with GCs alone

Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of upadacitinib versus the ACT for adults with GCA who are not candidates for therapy with GCs alone. An added benefit of upadacitinib in comparison with the ACT is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

[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].

Research question 1: Adults with GCA who are candidates for therapy with GCs alone

Overall, 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, there is no hint of an added benefit of upadacitinib over the ACT systemic GCs; an added benefit is therefore not proven.

Research question 2: Adults with GCA who are not candidates for therapy with GCs alone

Since no relevant study is available for the present research question, there is no hint of an added benefit of upadacitinib over the ACT; an added benefit is therefore not proven.

The result of the assessment of the added benefit of upadacitinib in comparison with the ACT is summarized in Table 3.

Table 3: 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	Therapy with systemic GCs	Added benefit not proven
2	Adults with GCA who are not candidates for therapy with glucocorticoids alone[b]	Therapy with systemic GCs in combination with tocilizumab	Added benefit not proven

a. Presented are the respective ACTs 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 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 was to assess the added benefit of upadacitinib compared with the ACT in adult patients with GCA.

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 upadacitinib

Research question	Therapeutic indication	ACT[a]
1	Adults with GCA who are candidates for therapy with glucocorticoids alone	Therapy with systemic GCs
2	Adults with GCA who are not candidates for therapy with glucocorticoids alone[b]	Therapy with systemic GCs in combination with tocilizumab

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 company followed the G-BA's specification of the ACT for both research questions.

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 to derive the added benefit. This concurred with the company’s inclusion criteria.

I 3 Research question 1: adults with GCA who are candidates for therapy with GCs alone

I 3.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on upadacitinib (status: 24 March 2025)
- Bibliographical literature search on upadacitinib (last search on 18 February 2025)
- Search in trial registries/trial results databases for studies on upadacitinib (last search on 27 February 2025)
- Search on the G-BA website for upadacitinib (last search on 27 February 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on upadacitinib (last search on 26 May 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: upadacitinib vs. GCs

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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
M16-852 (SELECT-GCA[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

GCs: glucocorticoids; RCT: randomized controlled trial

I 3.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SELECT-GCA	RCT, double-blind, parallel	Adults (≥ 50 years) with new-onset[b] or recurrent[a] active GCA[d, e] ▪ treatment with ≥ 40 mg prednisone (or equivalent) before the start of the study and treatment with ≥ 20 mg/day prednisone/prednisolone at the start of the study ▪ sufficiently clinically stable[f] for the GC tapering scheme defined in the study protocol	Upadacitinib 15 mg + GCs[g] (N = 209) upadacitinib 7.5 mg + GCs[g] (N = 107)[h] placebo + GCs[i] (N = 112) relevant subpopulation thereof[j]: upadacitinib 15 mg + GCs (n = 148) placebo + GCs (n = 76)	Screening: at most 35 days treatment: ▪ period 1: 52 weeks ▪ period 2[k]: 52 weeks follow-up: 30 days[i]	100 centres in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Portugal, Russia, Spain, Sweden, Switzerland, United Kingdom, United States 02/2019–04/2025 data cut-offs: 06 February 2024[m] 03 April 2025[n]	Primary: sustained remission from Week 12 to Week 52 secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs (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. Diagnosis ≤ 8 weeks prior to study start.
c. Recurrent GCA had to be diagnosed ≤ 8 weeks before the start of the study and was defined on the basis of the following criteria: active GCA and at least one unsuccessful attempt to taper GC therapy.
d. GCA diagnosis had to be based on the following criteria: age ≥ 50 years; ESR ≥ 50 mm/h or history of high-sensitivity C-reactive protein (hsCRP) ≥ 1 mg/dL; presence of clear cranial GCA symptoms (new onset of local headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischaemia-related loss of vision or otherwise unexplained mouth or jaw pain on chewing) and/or polymyalgia rheumatica (PMR) symptoms (shoulder and/or pelvic girdle pain associated with inflammatory morning stiffness); biopsy of the temporal artery shows GCA features and/or evidence of large vessel vasculitis (by means of angiography, cross-sectional imaging [e.g. MRI, CT or PET] or ultrasound of the temporal arteries, each assessed by a qualified radiologist or physician experienced in the assessment of large vessel vasculitis).
e. Active disease was defined by the following criteria: ESR ≥ 30 mm/h or an hsCRP value ≥ 1 mg/dL and the presence of at least one of the following criteria: definite cranial GCA symptoms, PMR symptoms or other signs of GCA or PMR flares as assessed by the investigator.
f. As assessed by the investigator.
g. As a 26-week GC tapering scheme; after discontinuation of GCs up to Week 26 upadacitinib was continued as monotherapy until Week 52.
h. The arm is irrelevant for the assessment and is no longer presented in the following tables.
i. As a 52-week GC tapering scheme.
j. Patients with new-onset GCA.
k. Blinded extension phase for patients who met the criteria for remission since at least Week 24 or had no symptoms or signs of GCA at Week 52 and were GC-free. Patients were either treated in the arm already allocated to them or they were re-randomized. Period 2 was not relevant for the present benefit assessment.
l. Outcomes in the morbidity categories were recorded until Week 52 in Period 1. The outcomes in the adverse events category were recorded up to 30 days after the end of treatment.
m. At the end of Period 1 (Week 52).
n. Final data cut-off at the end of the study after completion of Period 2 (Week 104).

AE: adverse event; CT: computed tomography; GC: glucocorticoid; ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; hsCRP: high-sensitivity C-reactive protein; MRI: magnetic resonance imaging; N: number of randomized patients; PET: positron emission tomography; PMR: polymyalgia rheumatica; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs (multipage table)

Study	Intervention	Comparison
SELECT-GCA	Upadacitinib 15 mg once daily, orally	Placebo once daily, orally
	Dose adjustment ▪ dose adjustments were not allowed. ▪ treatment interruption/discontinuation was permitted in the event of toxicity. ▪ treatment could be discontinued after ≥ 2 weeks of rescue therapy[a]	
	GC therapy (prednisone/prednisolone)	
	▪ Starting dose at the start of the study: ≥ 20 to 60 mg, once daily, orally ▪ from Week 1: gradual tapering until Week 26[b, c]	▪ Starting dose at baseline: ≥ 20 to 60 mg, once daily, orally ▪ from Week 1: gradual tapering until Week 52[b, c]
	Required pretreatment ▪ oral GCs: prednisone (or equivalent) ≥ 40 mg once daily at any time prior to the start of the study, and ≥ 20 mg prednisone or prednisolone once daily at the start of the study **permitted concomitant treatment** ▪ prednisone/prednisolone as rescue therapy[a] ▪ platelet aggregation inhibitors (acetylsalicylic acid, clopidogrel) ▪ oral calcium (1200 mg to 1500 mg) and vitamin D supplements (800 to 1000 IU) and/or bisphosphonates **non-permitted prior and concomitant treatment** ▪ JAK inhibitors (before study start and during the course of the study); IL-6 inhibitors (≤ 4 weeks before study start)[d]; other biologic and non-biologic DMARDs (≤ 5 times the mean terminal elimination half-life or without adherence to wash-out phases defined in the study protocol[e]) ▪ strong CYP3A inhibitors (from screening) or strong CYP3A inducers (≤ 30 days before first dose) ▪ systemic GC therapy over a period of > 4 years before the start of the study[f] ▪ oral GCs for an indication other than GCA or intravenous GCs (≤ 4 weeks prior to the start of the study) and not more than 2 cycles of systemic GC therapy for another indication (≤ 1 year prior to the start of the study)[g]; intra-articular, trigger point/tender point injections, intrabursal or epidural administration (study period 1) of GCs ▪ live vaccines (≤ 4 weeks before first dose to 4 weeks after last dose of study medication)[h]	

Table 7: Characteristics of the intervention – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs (multipage table)

Study	Intervention	Comparison
a. In the event of GCA recurrence or if the patient was unable to follow the tapering scheme, the tapering scheme was interrupted and prednisone/prednisolone was administered unblinded as rescue therapy. b. Depending on the GC starting dose, there was a first unblinded tapering phase of varying duration up to a dose of 20 mg. Subsequently, the GC tapering was blinded. In order to maintain blinding after completed tapering, the patients received a placebo from this point onwards. c. The exact tapering schedules for prednisone/prednisolone in both study arms are shown in I Appendix B. d. Patients who had previously been treated with an IL-6 inhibitor were not allowed to have experienced a disease flare during treatment. e. Anakinra (≤ 1 week prior to the start of the study); methotrexate, hydroxychloroquine, cyclosporine, azathioprine or mycophenolate (≤ 4 weeks prior to the start of the study); leflunomide (≥ 8 weeks, unless an elimination procedure was used); cell-depleting agents or alkylating agents, including cyclophosphamide (< 6 months prior to the start of the study). f. In addition, according to the investigator's assessment, there should be no inability to discontinue GC therapy according to the tapering schedule specified in the study protocol for a period of ≤ 4 years. g. GCs in other indications (inhaled or nasal; in stable doses ≥ 4 weeks before the start of the study) and short-term use (≤ 10 days) of GCs (oral, inhaled, nasal, intravenous, intramuscular) in other indications (cumulative dose ≤ 100 mg within 52 weeks) were permitted. h. For patients in Japan: ≤ 8 weeks before the first dose to 8 weeks after last dose of study medication. CYP: cytochrome P450; DMARD: disease-modifying antirheumatic drug; GC: glucocorticoids; GCA: giant cell arteritis; IL: interleukin; IU: international unit; JAK: Janus-associated kinase; RCT: randomized controlled trial		

Study design

The SELECT-GCA study is a completed, double-blind, multicentre, triple-arm RCT comparing 15 mg upadacitinib + GCs, 7.5 mg upadacitinib + GCs and placebo + GCs in adults with new-onset or recurrent active GCA. Patients had to have been treated with ≥ 40 mg prednisone (or equivalent) at any time in the past, and with ≥ 20 mg prednisone/prednisolone at the start of the study. Patients also had to have sufficient clinical stability for the GC tapering schedule specified in the study protocol as assessed by the investigator. Patients with certain infectious diseases specified in the study protocol, uncontrolled arterial hypertension or cardiovascular events (within the last 6 months) were excluded from the study. In addition, patients were not allowed to have any allergies or intolerances to GC, a component of the study medication, and/or other products in the same substance class.

A total of 428 patients were included in the study and randomly allocated in a 2:1:1 ratio to the treatment arms upadacitinib 15 mg + GCs (N = 209), upadacitinib 7.5 mg + GCs (N = 107) and placebo + GCs (N = 112). Randomization was stratified according to GC dose at baseline (prednisone/prednisolone > 30 mg vs. prednisone/prednisolone ≤ 30 mg), previous treatment with an IL-6 inhibitor (yes vs. no) and disease status at baseline (new-onset GCA vs. recurrent GCA). Deviating from this, the company states that randomization in Japan was not stratified due to the small number of patients. At the end of the 52-week double-blind phase, patients who met the criteria for sustained remission (see Table 11) from Week 24 or who had no

symptoms or signs of GCA at Week 52 and were GC-free could participate in a blinded 52-week extension phase. For this purpose, patients were either treated in the arm already allocated to them or they were re-randomized. Due to the re-randomization and the associated selection of patients, the results of this extension phase are not relevant for this benefit assessment.

The dosage of 7.5 mg upadacitinib per day is not covered by the marketing authorization. The upadacitinib 7.5 mg + GCs arm is thus irrelevant for this benefit assessment and is not addressed hereinafter. Treatment with upadacitinib in the upadacitinib 15 mg + GCs arm (hereinafter referred to as the intervention arm) followed the specifications of the SmPC [7]. In the comparator arm, patients received an analogue therapy with placebo. In the two relevant study arms, GCs were tapered according to a predetermined schedule (see I Appendix B). A first unblinded tapering phase of varying duration up to a daily dose of 20 mg took place depending on the starting dose. Subsequently, GCs were completely tapered in a blinded regimen by Week 26 at the latest in the intervention arm and Week 52 in the comparator arm. In order to maintain blinding after completed tapering, the patients received a placebo from this point onwards. In the event of GCA recurrence or if the patient was unable to follow the tapering schedule, tapering was interrupted and prednisone/prednisolone was administered unblinded as rescue therapy so that the daily GC dose was at least 20 mg.

The primary outcome of the study was sustained remission from Week 12 to Week 52, defined as the absence of signs or symptoms of GCA and adherence to the GC tapering schedule specified in the study protocol. Moreover, outcomes were recorded in the categories morbidity, health-related quality of life and AEs.

Relevant subpopulation

In this therapeutic indication, the G-BA differentiates between adult patients with GCA who are candidates for systemic therapy with GCs alone (research question 1) and those who are not candidates for systemic therapy with GCs alone (research question 2). According to the G-BA's information, 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. Accordingly, research question 1 particularly comprises patients with new-onset GCA who tolerate GC therapy and are not at high risk of GC-induced side effects. According to the S2k guideline of the German Society for Rheumatology and Clinical Immunology (Deutsche Gesellschaft für Rheumatologie und Klinische Immunologie [DGRh]) and the recommendations of the EULAR, there is an increased risk of GC-induced or GC-aggravated side effects and complications in patients with existing infectious diseases, cardiovascular events, arterial hypertension, diabetes mellitus, osteoporosis, weight gain, glaucoma, cataracts and adrenal insufficiency [8,9].

The SELECT GCA study included patients with new-onset or recurrent active GCA. For the assessment of research question 1, the company presented a subpopulation in its dossier that only included patients with new-onset GCA. This subpopulation comprised 148 patients in the intervention arm and 76 in the comparator arm. According to the company, this population is suitable to adequately derive the added benefit for research question 1. The company justified this with the fact that in the subpopulation presented by it, those patients were excluded who had a relapse and could therefore be assigned to research question 2 according to the G-BA's information. Since disease status (new-onset GCA vs. recurrent GCA) was used as a stratification factor in the SELECT-GCA study, the company argues that this approach does not violate randomization. According to the company, patients who did not tolerate GC therapy or had existing cardiovascular diseases, arterial hypertension or infectious diseases as comorbidities were also excluded from participation in the SELECT-GCA study. Patients who were intolerant to GC therapy or who were not candidates for therapy with GCs alone due to these comorbidities were therefore largely excluded from the study population. However, in the subpopulation presented by the company, a total of 29% vs. 36% of patients had at least one of the other comorbidities mentioned in the guidelines that are associated with an increased risk of GC-induced side effects (osteoporosis, diabetes mellitus, cataract, glaucoma and adrenal insufficiency). The company argues that no effect modifications were found in the results of the relevant outcomes for the characteristic comorbidities (yes vs. no), and that the results of the subgroup “comorbidity - no” were consistent with the results of the subpopulation for research question 1. Therefore, the presented subpopulation could be used to derive the added benefit of research question 1.

Concurring with the company, the subpopulation presented was used for the assessment of the added benefit for research question 1. However, despite the absence of effect modifications for the characteristic comorbidities (yes vs. no), there is uncertainty as to whether all patients in the subpopulation presented by the company were candidates for therapy with GCs alone. This uncertainty was taken into account in the assessment of the certainty of conclusions.

Individual aspects of the company's argumentation are commented on below:

Arterial hypertension

The company states that patients with arterial hypertension were excluded from the SELECT-GCA study. According to the study documents, however, 56% of patients in the intervention arm and 46% in the comparator arm have a history of hypertension or essential hypertension (based on the total population). Corresponding proportions are not available for the subpopulation presented. However, it is assumed that these proportions do not differ relevantly from the proportions in the total population. However, according to the inclusion and exclusion criteria of the SELECT-GCA study, only patients with uncontrolled arterial

hypertension were excluded. According to the marketing authorization for prednisone/prednisolone, there are special warnings for the treatment of patients with resistant hypertension. For these patients, treatment with prednisone/prednisolone is only recommended under strict indication establishment and supervision [10,11]. Based on the available information, it is generally assumed that the patients included in the SELECT-GCA study had controlled hypertension. As there are no specific warnings for patients with controlled hypertension, it is assumed that these patients are candidates for therapy with GCs alone.

Weight gain

The company argues that the guidelines do not contain any recommendations for specific BMI values at which therapy with GCs alone is no longer an option. Furthermore, only baseline weight and BMI data were available in the SELECT-GCA study, and weight gain during the SELECT-GCA study was not recorded. Therefore, weight gain is not a relevant comorbidity. Patients' body weight should be monitored during treatment with GCs [12]. However, it is assumed that patients may still be candidates for therapy with GCs alone despite weight gain. The potential inclusion of these patients in the presented subpopulation and their lack of consideration in the subgroup analysis of the company therefore has no consequences.

Summary

The subpopulation of patients with new-onset GCA presented by the company is relevant for the benefit assessment of upadacitinib. However, there remains uncertainty as to whether all patients are candidates for therapy with GC alone. This uncertainty was taken into account in the assessment of the certainty of conclusions.

Data cut-offs

According to information provided by the company in Module 4 A, 2 data cut-offs are available for the SELECT-GCA study:

- Data cut-off: 06 February 2024, at the end of Period 1 (Week 52)
- Data cut-off: 03 April 2025, final data cut-off at the end of the study after completion of Period 2 (Week 104)

The data cut-off of 06 February 2024 is used for this benefit assessment. This concurs with the company’s approach.

Characteristics of the relevant subpopulation

Table 8 shows the characteristics of the patients in the subpopulation of SELECT-GCA relevant for the benefit assessment.

Table 8: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: upadacitinib + GCs versus placebo + GCs (multipage table)

Study characteristic category	Upadacitinib + GC N = 148	Placebo + GC N = 76
SELECT-GCA		
Age [years], mean (SD)	71 (7)	72 (7)
Sex [F/M], %	76/24	64/36
Geographical region, n (%)		
North America	6 (4)	7 (9)
Western Europe	100 (68)	37 (49)
Eastern Europe	8 (5)	8 (11)
Asia	9 (6)	4 (5)
Oceania	25 (17)	20 (26)
Disease duration since diagnosis [weeks], mean (SD)	5.7 (4.2)[a]	5.2 (2.1)[a]
Ischaemia-related loss of vision[b], n (%)		
Yes	18 (12)	22 (29)
No	130 (88)	54 (71)
GC dose at baseline [mg]		
Mean (SD)	37.9 (11.9)	37.9 (10.5)
≤ 30 mg, n (%)	61 (41)	30 (39)
> 30 mg, n (%)	87 (59)	46 (61)
History of clear symptoms of PMR without cranial GCA symptoms, n (%)		
Yes	10 (7)	11 (14)
No	138 (93)	65 (86)
ESR at baseline [mm/h], mean (SD)	17.9 (16.5)	22.2 (29.5)
CRP at baseline [mg/L][c], mean (SD)	6.9 (13.6)	5.8 (9.4)
Comorbidities[d], n (%)		
Yes	43 (29)	27 (36)
No	105 (71)	49 (64)
Treatment discontinuation, n (%)[e]	38 (26)	25 (33)
Study discontinuation, n (%)[f]	24 (16)	17 (22)

a. Institute's calculation.
b. Within eight weeks from baseline.
c. Implausible information in Module 4 A; it is assumed that the values are not in mg/dL but in mg/L.
d. The following comorbidities were included: osteoporosis, diabetes mellitus, cataracts, glaucoma and adrenal insufficiency.
e. Common reasons for treatment discontinuation in the intervention arm vs. control arm were the following (percentages based on randomized patients): AEs (17% vs. 20%), lack of efficacy (3% vs. 8%).
f. Common reasons for study discontinuation in the intervention vs. the control arm were the following (percentages based on randomized patients): AEs: (10% vs. 13%), patient's request (4% vs. 4%).

Table 8: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: upadacitinib + GCs versus placebo + GCs (multipage table)

Study characteristic category	Upadacitinib + GC N = 148	Placebo + GC N = 76
AE: adverse event; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; f: female; GC: glucocorticoid; GCA: giant cell arteritis; m: male; n: number of patients in the category; N: number of randomized patients; PMR: polymyalgia rheumatica; RCT: randomized controlled trial; SD: standard deviation		

Patient characteristics were largely balanced between the two treatment arms of the SELECT-GCA study. The mean age of the patients was 71 years, they were predominantly female (72%), and were mostly enrolled in Western Europe (68% vs. 49%) and Oceania (17% vs. 26%). Ischaemia-related loss of vision occurred more frequently in the comparator arm than in the intervention arm (12% vs. 29%). The GC dose at the baseline was 37.9 mg/day in both study arms. A history of clear symptoms of PMR without cranial GCA symptoms was reported in 7% of patients in the intervention arm and 14% in the comparator arm. Overall, comorbidities occurred more seldom in in the intervention arm than in the comparator arm (29% vs. 36%).

Treatment was discontinued less frequently in the intervention arm than in the comparator arm (26% vs. 33%). In both study arms, the most common reasons for treatment discontinuation were AEs (17% vs. 20%). A total of 16% vs. 22% of patients discontinued the study. Here again, the most common reasons for study discontinuation were AEs (10% versus 13%).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs

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			
SELECT-GCA	Yes	Yes	Yes	Yes	Yes	Yes	Low
GCs: glucocorticoids; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the SELECT-GCA study.

Transferability of the study results to the German health care context

The company states that approximately 61% of the study population consisted of participants from Western Europe. Due to the structural equality between the study population and the target population in the therapeutic indication, particularly with regard to clinical parameters, it can be assumed, according to company, that the clinical effects observed in the SELECT-GCA study also occur in health care under everyday condition. Therefore, the study results are transferable to the German health care context. In addition, the company states that it cannot identify any indications that would contradict a transferability.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Remission
  - Fatigue, recorded with the FACIT-Fatigue
  - Health status, recorded using the EQ-5D VAS
  - Symptoms recorded with the PGIC instrument
- Health-related quality of life
  - Recorded with the SF-36
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Infections (System Organ Class [SOC], AE)
  - Serious infections (SOC, SAEs)
  - 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 A).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs

Study	Outcomes											
	All-cause mortality[a]	Remission	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Symptoms (PGIC)	Health-related quality of life (SF-36)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Infections (SOC, AEs)	Serious infections (SOC, SAEs)	Other specific AEs
SELECT-GCA	Yes	No[c]	No[c]	No[c]	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	No[d]

a. Deaths were recorded as AEs.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. No suitable data available; see body of text for reasons.
d. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT: Functional Assessment of Chronic Illness Therapy; GCs: glucocorticoids; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes

Remission

Analyses on remission presented by the company

In Module 4 A 4, the company presents four different analyses for the outcome remission, which differ in terms of the outcome components included and the analysis date considered. According to operationalization, patients were only classified as responders if all outcome components included were met in each case. A summary of the operationalizations of remission presented by the company and the outcome components considered therein is shown in Table 11.

Table 11: Operationalizations presented by the company on the remission and the individual components considered therein

	Remission	**Complete remission**	**Sustained remission**	**Sustained complete remission**
Date of analysis	At Week 52	At Week 52	From Week 12 to Week 52	From Week 12 to Week 52
Symptoms	Presence of signs and symptoms of GCA[a]			
GC therapy	Compliance with the GC tapering schedule specified in the study protocol, i.e. classification as a non-responder upon initiation of rescue therapy with GCs or receipt of more than 100 mg of additional systemic GCs (prednisone equivalent dose) for the therapeutic indication GCA, without this being identified as rescue therapy.			
Laboratory parameters		Normalization of ESR (< 30 mm/h)[b], normalization of CRP (< 1 mg/dL)		Normalization of ESR (< 30 mm/h)[b], normalization of CRP (< 1 mg/dL) and no increase to ≥ 1 mg/dL on 2 consecutive visits

a. Individual components in isolation cannot be used as remission outcomes, as it cannot be ruled out that the absence of GCA symptoms or signs is associated with an increased GC dose and thus with an increased risk of GC-associated side effects. The analyses on the individual component symptoms are presented as supplementary information in I Appendix C of the full dossier assessment.
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

Outcome component "Compliance with the GC tapering schedule specified in the study protocol"

In the SELECT-GCA study, patients had to adhere to a tapering schedule for discontinuing GC therapy specified in the study protocol (see I Appendix B of the full dossier assessment) in order to be considered responders for the operationalization of the outcome remission. Based on the individual starting dose for each patient (20 mg to 60 mg per day), this prescribed tapering schedule provided for complete discontinuation of GC therapy in the intervention arm between Week 20 and Week 26. In the comparator arm, this period was between Week 46 and Week 52. The individualized starting dose of 20 mg to 60 mg GCs per day and the planned tapering schedule largely concur with the recommendations in the guidelines. However, the reduction of the GC dose in the SELECT-GCA study is somewhat faster than described in the guidelines, which specify a target dose of ≤ 5 mg/day at Week 52 [8,9].

The outcome component "adherence to the GC tapering schedule specified in the study protocol" is not assessed as an adequate component of the remission outcome as any deviation from the prescribed tapering schedule led to a classification as non-responder and thus constituted an exclusion criterion for achieving remission. The S2k guideline describes that GC reduction and complete tapering should be determined on an individual basis for each patient under clinical and laboratory supervision [9]. Individualized dose adjustment during

GC tapering was possible in the SELECT-GCA study in the form of administration of GCs as rescue therapy (≥ 20 mg GCs per day) when signs and symptoms of GCA occurred or when patients were unable to adhere to the prescribed GC tapering schedule for other reasons. However, this individualized adjustment meant that patients were classified as non-responders and consequently no longer met the criteria for remission (see Table 11). The assumption implicitly made by the company's operationalizations that patients who have received rescue therapy cannot achieve remission between Week 12 and Week 52 and are therefore ultimately classified as non-responders is not appropriate. Especially with rescue therapy administered early in the course of the disease, remission is still possible for these patients.

In order to address the reduction in GC requirements in remission analyses, it is generally advisable to consider the achievement of a relevant steroid threshold value in addition to symptoms as a component of the remission outcome. The choice of a steroid threshold value should be justified and selected in such a way that it is possible for almost all patients to achieve it during the analysis period under consideration. For example, EULAR also includes the achievement of an individual GC target dose rather than adherence to a fixed tapering schedule in its definition of sustained remission [8].

Outcome component "Normalization of ESR and normalization of CRP"

The outcomes on complete remission and sustained complete remission include the laboratory markers ESR and CRP, which are not necessarily accompanied by noticeable symptoms for the patient [8,9]. Elevated inflammatory parameters may also suggest the presence of infectious diseases, for example. Furthermore, Kermani et al. reported that in their prospective cohort study, 21% of symptomatic GCA recurrences did not show an increase in ESR and CRP values [13]. The GiACTA study also reported symptomatic recurrence without elevated ESR and CRP levels in 34% of patients treated with prednisolone. In contrast, the same study provided proof of elevated CRP levels in over 50% of patients treated with prednisolone, even without the presence of a recurrence [14].

Furthermore, acute phase proteins such as CRP may react independently of clinical improvement when antibodies against IL-6 receptors, JAK inhibitors or tumour necrosis factor (TNF) inhibitors are used [15-18]. Therefore, an improvement in laboratory parameters does not necessarily reflect a clinical improvement in the patient's symptoms. If normalization of CRP levels is included in the outcome definition of remission, remission could 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. The inclusion of laboratory parameters in the definition of remission might lead to an unfair comparison in favour of the intervention arm. The analyses presented, which include the normalization of ESR and CRP, are therefore not suitable for the benefit assessment.

Replacement strategy chosen by the company

According to the company, patients who discontinued the study medication prematurely were imputed as non-responders for the remission analyses presented in Module 4 A. Multiple imputation was planned for patients who received more than 100 mg of systemic GCs for a condition other than GCA. In addition, the company states that patients are still considered responders even if a value is missing, provided that they were classified as responders at the visits before and after the relevant point in time. Furthermore, only limited information is available on the missing and imputed values and on the reasons for the imputations for the subpopulation submitted by the company. Hence, the extent to which the chosen imputation of missing values is appropriate for this analysis remains unclear. In principle, patients who have received rescue therapy should not be imputed, but should be included in the analysis with their observed values.

Summary

In summary, a suitable operationalization for the recording of the outcome remission was not predefined in the SELECT-GCA study. All analyses on the remission outcomes submitted by the company can therefore not be used for the benefit assessment. An appropriate assessment of remission should cover the symptoms and could also take into account a steroid threshold value or steroid-free status (see e.g. A24-113 [19]). 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. A suitable analysis on the remission should be submitted by the company in the commenting procedure.

Recurrence

The company presented three analyses on the outcome recurrence in its dossier. In the SELECT-GCA study, recurrence was defined as an event that, in the investigator's opinion, represented the recurrence of signs and symptoms of GCA or an GCA-related increase in ESR to > 30 mm/h, requiring an increase in the GC dose. An increase in the GC dose was defined as rescue therapy initiated by the investigator for GCA or the receipt of additional systemic GCs for the indication RCA, which was administered as concomitant medication but did not constitute rescue therapy. For the reasons described above regarding the outcome remission, the change in the laboratory parameter ESR and the increase in the GC dose, which deviates from the prescribed GC tapering schedule, are not relevant to the patient. Since patients may either go into remission or experience a relapse, only the outcome remission is considered for this benefit assessment in order to avoid double recording of the same effect.

Patient-reported outcomes

General comment on submitted responder analyses for the patient-reported outcomes

For the patient-reported outcomes in the categories morbidity and health-related quality of life, which were recorded using FACIT-Fatigue, EQ-5D VAS, PGIC and SF-36, the company presents responder analyses for improvement in symptoms in M4. The response criteria used in the analyses presented by the company fulfil the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as described in the *General Methods* of the Institute [1]. In principle, responder analyses are to be preferred for the benefit assessment. However, for the present benefit assessment, it does not seem adequate to consider only responder analyses on improvement, as both improvement and deterioration are possible and relevant for patients in the therapeutic indication. For this reason, responder analyses should be considered in the present therapeutic situation in order to identify improvements and deteriorations. In addition, the CSR provides continuous analyses of the relevant subpopulation except for the outcome PGIC [3]. Continuous analyses are generally suitable for the benefit assessment, but in the analyses presented in the CSR, patients who received rescue therapy with GCs were classified as non-responders. This is not appropriate, as these patients can continue to contribute relevant data for the recording of outcomes (see below for the imputation strategy).

Symptoms (PGIC)

The PGIC consists of a single question asking the patient to assess the overall change in GCA-related symptoms (pain) since the start of treatment on a 7-point scale (from "very much improved" to "very much deteriorated"). The PGIC was recorded at Weeks 8, 12, 24 and 52. In its dossier, the company presents non-prespecified responder analyses for the assessment of any improvement and, in addition, prespecified analyses on strong improvement ("very much improved" and "much improved"). For the present assessment, it does not seem adequate to consider only responder analyses on improvement, as both improvement and deterioration are possible and relevant for patients in the therapeutic indication. 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 should be presented.

Proportion of missing values and imputation strategy chosen by the company

For the outcomes relating to general health status, symptoms and health-related quality of life, 36% to 43% of values are missing or imputed in the intervention arm and 54% to 62% in the comparator arm. The proportion of missing and imputed values in both treatment arms exceeds the proportion that can be explained by missing questionnaires (18% vs. 29% to 30%) or study discontinuations (16% vs. 22%). This additional proportion of missing and imputed values could be explained by NRI of those patients who started rescue therapy initiated by the investigator (23% vs. 42%). This imputation strategy is not appropriate. In particular, if patients

have received rescue therapy in the early course of treatment, improvement in symptoms is still possible up to Week 52. Due to the potentially high proportion of imputed patients who were classified as non-responders solely on the basis of the initiation of rescue therapy, and due to the different proportions of patients who initiated rescue therapy in the study arms (23% vs. 42%), the outcomes relating to general health status and health-related quality of life cannot be used for the benefit assessment. Furthermore, only limited information is available on the missing and imputed values and on the reasons for the imputations for the subpopulation presented by the company. Hence, the extent to which the chosen imputation of missing values is appropriate for this analysis remains unclear.

Side effects

The preferred term (PT) GCA was included in the analyses of the outcomes severe AEs and discontinuations due to AEs. This was not appropriate. However, as it can be assumed that this does not mask any significant effects (particularly to the disadvantage of the intervention), the analyses can still be used for the benefit assessment.

Furthermore, events such as the PTs headache and polymyalgia rheumatica or the SOC eye disorders, which can both be side effects or represent the progression of the underlying disease, are included in the outcome discontinuation due to AE. It cannot be conclusively clarified to what extent the events can be assigned to the outcome category of morbidity or side effects. This remains of no consequence for the present benefit assessment.

I 3.2.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs

Study	Outcomes												
	Study level	All-cause mortality[a]	Remission	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Symptoms (PGIC)	Health-related quality of life (SF-36)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Infections (SOC, AEs)	Serious infections (SOC, SAEs)	Other specific AEs
SELECT-GCA	L	H[c]	–[d]	–[d]	–[d]	–[d]	–[d]	H[c, e]	H[c, e]	L	H[c, e]	H[c, e]	–

a. Deaths were recorded as AEs.
b. Operationalized as CTCAE grade ≥ 3.
c. High proportion of treatment dropouts in the treatment arms and large difference in the proportion of treatment dropouts between the treatment arms.
d. See Section I 3.2.1 of this dossier assessment for reasoning.
e. Incomplete observations for potentially informative reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT: Functional Assessment of Chronic Illness Therapy; GCs: glucocorticoids; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; SF-36: Short Form (36) Health Survey; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the results on the outcome discontinuation due to AEs must be rated as low.

There is a high risk of bias for the outcome all-cause mortality. The reason for this is the high proportion of treatment dropouts in the treatment arms and the large difference in the proportion treatment dropouts between the treatment arms, as it is unclear whether these patients were followed up until Week 52.

For the remaining outcomes in the side effects category, there is a high risk of bias of the results. On the one hand, this is due to incomplete observations for potentially informative reasons. On the other hand, there is a large proportion of treatment dropouts in both treatment arms and a large difference in the proportion of treatment dropouts between the treatment arms.

Summary assessment of the certainty of conclusions

As already described in Section I 3.1.2, there is uncertainty in the subpopulation presented by the company with regard to the patient population included. In the subpopulation presented,

a total of 29% vs. 36% of patients had at least one comorbidity that is associated with an increased risk of GC-induced side effects (osteoporosis, diabetes mellitus, cataract, glaucoma and adrenal insufficiency). Despite the absence of effect modifications due to the characteristic comorbidity (yes vs. no), there is uncertainty as to whether all patients in the subpopulation presented by the company were candidates for therapy with GCs alone and can therefore be assigned to question 1. The certainty of conclusions is therefore restricted for all outcomes. Thus, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the effects shown in the SELECT-GCA study.

I 3.2.3 Results

Table 13 summarizes the results on the comparison of upadacitinib + GCs with placebo + GCs in patients with new-onset active GCA. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: upadacitinib + GCs vs. placebo + GCs

Study outcome category outcome	Upadacitinib + GC		Placebo + GC		Upadacitinib + GCs vs. placebo + GCs
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
SELECT-GCA					
Mortality					
All-cause mortality[b]	148	2 (1.4)	76	2 (2.6)	0.51 [0.07; 3.57]; 0.597
Morbidity					
Remission				No suitable data[c]	
Fatigue (FACIT-Fatigue)				No suitable data[c]	
Health status (EQ-5D VAS)				No suitable data[c]	
Symptoms (PGIC)				No suitable data[c]	
Health-related quality of life					
SF-36					
Physical Component Summary (PCS)				No suitable data[c]	
Mental Component Summary (MCS)				No suitable data[c]	
Side effects					
AEs (supplementary information)	148	147 (99.3)	76	72 (94.7)	–
SAEs	148	36 (24.3)	76	19 (25.0)	0.97 [0.60; 1.58]; 0.923
Severe AEs[d]	148	51 (34.5)	76	23 (30.3)	1.14 [0.76; 1.71]; 0.615
Discontinuation due to AEs	148	26 (17.6)	76	19 (25.0)	0.70 [0.42; 1.19]; 0.194
Infections (SOC, AEs)	148	96 (64.9)	76	42 (55.3)	1.17 [0.93; 1.48]; 0.172
Serious infections (SOC, SAEs)	148	9 (6.1)	76	8 (10.5)	0.58 [0.23; 1.44]; 0.309

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [20]).
b. Deaths were recorded as AEs.
c. See Section I 3.2.1 of this dossier assessment for the reasoning.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACIT: Functional Assessment of Chronic Illness Therapy; GCA: giant cell arteritis; GCs: glucocorticoids; MCS: Mental Component Summary; n: 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; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes. The reasons for this are described in Section I 3.2.2 in the Section "Relevant subpopulation".

Mortality

All-cause mortality

No statistically significant difference between treatment groups was found for the outcome overall survival. There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

Morbidity

Remission

No suitable data are available for the outcome remission (see Section I 3.2.1 for reasoning). There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

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

No suitable data are available for the outcomes fatigue, recorded using FACIT-Fatigue, health status, recorded using EQ-5D VAS, and symptoms, recorded using PGIC (for reasoning, see Section I 3.2.1). There is no hint of an added benefit of upadacitinib over GCs in each case; an added benefit is therefore not proven.

Health-related quality of life

SF-36

Health-related quality of life was recorded using the PCS and the MCS of the SF-36. No suitable data are available for health-related quality of life, measured using the SF-36 (for justification, see Section I 3.2.1). There is no hint of an added benefit of upadacitinib over GCs; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the outcomes SAEs, severe AEs and discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from upadacitinib in comparison with GCs; greater or lesser harm is therefore not proven.

Infections (AEs), serious infections (SAEs)

No statistically significant differences between the treatment arms were shown for the outcomes "infections" (AEs) and "serious infections" (SAEs). In each case, there is no hint of

greater or lesser harm from upadacitinib in comparison with GCs; greater or lesser harm is therefore not proven.

I 3.2.4 Subgroups and other effect modifiers

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

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

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.

In accordance with the described methods, no relevant effect modification by the characteristics of age or sex was identified for the outcomes for which suitable data are available.

In addition to the potential effect modifiers mentioned above, it is also useful to consider the characteristic comorbidity (yes vs. no) due to the uncertainties regarding the subpopulation for research question 1 (see Section I 3.1.2). The company presented subgroup analyses for patients with one or more comorbidities for its submitted subpopulation. The company defines osteoporosis, diabetes mellitus, cataracts, glaucoma and adrenal insufficiency as relevant comorbidities. The application of the methods described above for the outcomes for which suitable data are available also yielded no effect modifications for the characteristic comorbidities (yes vs. no).

I 3.3 Probability and extent of added benefit

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

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

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 3.2 (see Table 14).

Table 14: 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	No suitable data[c]	Lesser benefit/added benefit not proven
Fatigue (FACIT-Fatigue)	No suitable data[c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser benefit/added benefit not proven
Symptoms (PGIC)	No suitable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36 (PCS)	No suitable data[c]	Lesser benefit/added benefit not proven
SF-36 (MCS)	No suitable data[c]	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

Table 14: 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]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. See Section I 3.2.1 of this dossier assessment for the reasoning. 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		

I 3.3.2 Overall conclusion on added benefit

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

Table 15: Positive and negative effects from the assessment of upadacitinib in comparison with GCs

Positive effects	**Negative effects**
–	–
There are no suitable data for outcomes in the categories morbidity and health-related quality of life.	
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, there is no hint of an added benefit of upadacitinib over the ACT systemic GCs; an added benefit is therefore not proven.

The assessment described above deviates from that by the company, which derived an indication of major added benefit of upadacitinib in comparison with the ACT for these patients.

I 4 Research question 2: Adults with GCA who are not candidates for therapy with GCs alone

I 4.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on upadacitinib (status: 24 March 2025)
- Bibliographical literature search on upadacitinib (last search on 18 February 2025)
- Search in trial registries/trial results databases for studies on upadacitinib (last search on 27 February 2025)
- Search on the G-BA website for upadacitinib (last search on 27 February 2025)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 26 May 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no relevant study.

I 4.2 Results on added benefit

No data are available for the assessment of the added benefit of upadacitinib versus the ACT for adults with GCA for whom monotherapy with GCs is not an option. There is no hint of an added benefit of upadacitinib in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

In its dossier, the company presented no data for the assessment of the added benefit of upadacitinib versus the ACT for adults with GCA for whom monotherapy with GCs is not an option. An added benefit of upadacitinib in comparison with the ACT is therefore not proven.

The assessment described above concurs with that by the company.

I 5 Probability and extent of added benefit – summary

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

Table 16: Upadacitinib – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Adults with GCA for whom monotherapy with GCs is an option	Treatment with systemic GCs	Added benefit not proven
2	Adults with GCA for whom monotherapy with GCs is not an option[b]	therapy with systemic GCs in combination with tocilizumab	Added benefit not proven

a. Presented are the respective ACTs 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

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. AbbVie. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA; study M16-852; Clinical Study Report [unpublished]. 2024.

4. AbbVie Deutschland. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis [online]. 2024 [Accessed: 04.06.2025]. URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2023-505476-29-00.

5. AbbVie. A Study to Evaluate the Safety and Efficacy of Upadacitinib in Participants With Giant Cell Arteritis (SELECT-GCA) [online]. 2025 [Accessed: 04.06.2025]. URL: https://clinicaltrials.gov/study/NCT03725202.

6. Blockmans D, Penn SK, Setty AR et al. A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis. N Engl J Med 2025. https://doi.org/10.1056/NEJMoa2413449.

7. AbbVie. RINVOQ 15 mg/30 mg/45 mg Retardtabletten [online]. 04.2025 [Accessed: 15.05.2025]. URL: https://www.fachinfo.de.

8. Hellmich B, Agueda A, Monti S et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020; 79(1): 19-30. https://doi.org/10.1136/annrheumdis-2019-215672.

9. Schirmer JH, Aries PM, Balzer K et al. S2k Leitlinie Management der Großgefäßvaskulitiden [online]. 2020 [Accessed: 15.05.2025]. URL: https://register.awmf.org/assets/guidelines/060-007l_S2k_Management_Gro%C3%9Fgef%C3%A4%C3%9Fvaskulitiden_2020-08.pdf.

10. acis Arzneimittel. Prednison acis [online]. 03.2022 [Accessed: 27.06.2025]. URL: https://www.fachinfo.de.

11. acis Arzneimittel. Prednisolon acis [online]. 12.2024 [Accessed: 28.05.2025]. URL: https://www.fachinfo.de.

12. Hoes JN, Jacobs JW, Boers M et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2007; 66(12): 1560-1567. https://doi.org/10.1136/ard.2007.072157.

13. Kermani TA, Warrington KJ, Cuthbertson D et al. Disease Relapses among Patients with Giant Cell Arteritis: A Prospective, Longitudinal Cohort Study. J Rheumatol 2015; 42(7): 1213-1217. https://doi.org/10.3899/jrheum.141347.

14. Stone JH, Tuckwell K, Dimonaco S et al. Glucocorticoid Dosages and Acute-Phase Reactant Levels at Giant Cell Arteritis Flare in a Randomized Trial of Tocilizumab. Arthritis Rheumatol 2019; 71(8): 1329-1338. https://doi.org/10.1002/art.40876.

15. Smolen JS, Landewé RBM, Bergstra SA et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2023; 82(1): 3-18. https://doi.org/10.1136/ard-2022-223356.

16. Reisch M, Dejaco C. [Methods for assessment of disease activity of polymyalgia rheumatica]. Z Rheumatol 2023; 82(5): 368-379. https://doi.org/10.1007/s00393-023-01358-x.

17. Chikhoune L, Poggi C, Moreau J et al. JAK inhibitors (JAKi): Mechanisms of action and perspectives in systemic and autoimmune diseases. Rev Med Interne 2025; 46(2): 89-106. https://doi.org/10.1016/j.revmed.2024.10.452.

18. Smolen JS, Aletaha D, Gruben D et al. Brief Report: Remission Rates With Tofacitinib Treatment in Rheumatoid Arthritis: A Comparison of Various Remission Criteria. Arthritis Rheumatol 2017; 69(4): 728-734. https://doi.org/10.1002/art.39996.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Benralizumab (eosinophile Granulomatose mit Polyangiitis); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 27.06.2025]. URL: https://doi.org/10.60584/A24-113.

20. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under
https://www.iqwig.de/en/projects/a25-66.html