ORIGINAL ARTICLE

A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis

Daniel Blockmans, M.D., Ph.D.,[1,2] Sara K. Penn, M.D.,[3] Arathi R. Setty, M.D., M.P.H.,[3] Wolfgang A. Schmidt, M.D., M.A.C.R.,[4] Andrea Rubbert-Roth, M.D.,[5] Ellen M. Hauge, M.D., Ph.D.,[6,7] Helen I. Keen, M.B., B.S., Ph.D.,[8] Tomonori Ishii, M.D., Ph.D.,[9] Nader Khalidi, M.D.,[10] Christian Dejaco, M.D., Ph.D.,[11,12] Maria C. Cid, M.D.,[13] Bernhard Hellmich, M.D.,[14] Meng Liu, Ph.D.,[3] Weihan Zhao, Ph.D.,[3] Ivan Lagunes, M.D.,[3] Ana B. Romero, M.D.,[3] Peter K. Wung, M.D., M.H.S.,[3] and Peter A. Merkel, M.D., M.P.H.,[15] for the SELECT-GCA Study Group*

ABSTRACT

BACKGROUND

Giant-cell arteritis is a systemic vasculitis with limited treatment options. The efficacy and safety of upadacitinib — a selective Janus kinase (JAK) inhibitor that blocks the signaling of several cytokines, including interleukin-6 and interferon-γ — are unknown in patients with giant-cell arteritis.

METHODS

We randomly assigned patients with new-onset or relapsing giant-cell arteritis, in a 2:1:1 ratio, to receive upadacitinib at a dose of 15 mg or 7.5 mg orally once daily plus a 26-week glucocorticoid taper or placebo plus a 52-week glucocorticoid taper. The primary end point was sustained remission at week 52, defined by the absence of signs or symptoms of giant-cell arteritis from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper.

RESULTS

A total of 209 patients received upadacitinib at a dose of 15 mg, 107 received upadacitinib at a dose of 7.5 mg, and 112 received placebo; 70% of the patients had new-onset giant-cell arteritis. Upadacitinib at a dose of 15 mg showed superiority over placebo with respect to the primary end point (46.4% [95% confidence interval {CI}, 39.6 to 53.2] vs. 29.0% [95% CI, 20.6 to 37.5]; P=0.002). Upadacitinib at a dose of 15 mg was superior to placebo in the analysis of the hierarchically prespecified and multiplicity-controlled key secondary end points of sustained complete remission, time to a disease flare, cumulative glucocorticoid exposure, and patient-reported outcomes. Upadacitinib at a dose of 7.5 mg was not superior to placebo with respect to the primary end point (41.1% [95% CI, 31.8 to 50.4]). Safety outcomes during the treatment period of 52 weeks were similar in the upadacitinib and placebo groups. Although cardiovascular risk is a potential concern with a JAK inhibitor, no major adverse cardiovascular events occurred in the upadacitinib groups.

CONCLUSIONS

In patients with giant-cell arteritis, upadacitinib at a dose of 15 mg — but not 7.5 mg — with a 26-week glucocorticoid taper showed efficacy superior to that of placebo with a 52-week glucocorticoid taper. (Funded by AbbVie; SELECT-GCA ClinicalTrials.gov number, NCT03725202.)

Author affiliations are listed at the end of the article. Prof. Blockmans can be contacted at daniel.blockmans@uzleuven.be or at the University Hospital Gasthuisberg, Department of General Internal Medicine, Herestraat 49, 3000 Leuven, Belgium.

*A full list of the SELECT-GCA Study Group members is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 2, 2025, and updated on June 6, 2025, at NEJM.org.

N Engl J Med 2025;392:2013-24.
DOI: 10.1056/NEJMoa2413449

CME

A Quick Take is available at NEJM.org

Giant-cell arteritis is a vascular inflammatory disease that primarily affects large and medium-sized arteries, particularly the cranial branches of the aorta. The disease affects almost exclusively adults 50 years of age or older, with a mean age of more than 70 years, and more commonly occurs in women than in men.[1,2] Giant-cell arteritis is the most common primary vasculitis in adults, with a global pooled prevalence of 51 cases per 100,000 persons older than 50 years of age.[3] Manifestations of giant-cell arteritis include headaches, scalp or temple pain or tenderness, jaw claudication, vision impairment, and other ischemic complications. Polymyalgia rheumatica is associated with giant-cell arteritis, and many patients have overlapping symptoms.[4] Only one therapy for the disease is approved (tocilizumab, an interleukin-6 receptor inhibitor[5]), and glucocorticoids remain the primary treatment option despite the high risk of glucocorticoid-related toxic effects. Approximately 50 to 80% of patients with giant-cell arteritis have a disease relapse when glucocorticoids are tapered.[6] Thus, there is an unmet need for effective, glucocorticoid-sparing treatments for this disease.

Interleukin-6 and interferon-γ play major roles in the pathogenesis of giant-cell arteritis and signal through the JAK–STAT (Janus kinase–signal transducer and activator of transcription) pathway.[7,8] Upadacitinib, an oral and selective Janus kinase (JAK)-1 inhibitor,[9] has the potential to block multiple pathogenic pathways in giant-cell arteritis[10,11] and received approval for the treatment of several immune-mediated inflammatory diseases.[12-17] Reported here are the primary results through week 52 of the SELECT-GCA phase 3 trial assessing the efficacy and safety of upadacitinib as compared with placebo, when used in combination with a glucocorticoid taper, to treat patients with active giant-cell arteritis.

METHODS

TRIAL DESIGN AND PATIENTS

This trial was conducted at 100 sites in 24 countries and included two 52-week periods: a randomized, double-blind treatment period followed by an extension period (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We report here the results from the first 52-week treatment period. Eligible patients were adults 50 years of age or older who had a clinical diagnosis of new-onset or relapsing giant-cell arteritis confirmed by temporal-artery biopsy or imaging (ultrasonography, positron-emission tomography, computed tomography, magnetic resonance imaging, or angiography) and in whom the disease was active within 8 weeks before the baseline visit. Active giant-cell arteritis was defined by the presence of unequivocal cranial symptoms of the disease, polymyalgia rheumatica, or both, along with an erythrocyte sedimentation rate (ESR) of at least 30 mm per hour, a C-reactive protein (CRP) level of at least 1 mg per deciliter, or both. New-onset disease referred to the diagnosis of giant-cell arteritis within 8 weeks before baseline; relapsing disease was defined as the reactivation of the disease in patients for whom at least 1 glucocorticoid taper failed to control the disease. At any time before enrollment, patients must have received prednisone at a dose of at least 40 mg daily (or equivalent); at baseline, patients must have been receiving prednisone at a dose of 20 to 60 mg daily. Patients with previous exposure to JAK inhibitors or who had had a disease flare while receiving an interleukin-6 inhibitor were excluded (full eligibility criteria can be found in Section S2).

Randomization was performed with the use of an interactive-response system. The patients were randomly assigned, in a 2:1:1 ratio, to receive upadacitinib at a dose of 15 mg or 7.5 mg once daily in combination with a prespecified 26-week glucocorticoid taper or placebo with a prespecified 52-week glucocorticoid taper (Table S1). The glucocorticoid taper regimen was open-label until the dose reached 20 mg per day, after which it was blinded. The glucocorticoid taper regimens were tailored to each patient on the basis of the starting dose, with the patients in the upadacitinib groups discontinuing by week 26 and those in the placebo group discontinuing by week 52.

TRIAL OVERSIGHT

The trial was conducted in accordance with the International Council for Harmonisation guidelines, applicable regulations, and the principles of the Declaration of Helsinki. The protocol, available at NEJM.org, was approved by an independent ethics committee or institutional review board at each trial site. All the patients provided written informed consent.

The sponsor (AbbVie) designed the trial, and the investigators and sponsor jointly gathered and interpreted the data. The sponsor analyzed the data and provided medical writing support. All the authors reviewed and approved the manuscript, had access to the data, made the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the data, the fidelity of the trial to the protocol, and the accuracy of the reporting of adverse events.

END POINTS AND SAFETY ASSESSMENTS

The primary end point was sustained remission at week 52, defined by the absence of signs or symptoms of giant-cell arteritis from week 12 through week 52 and adherence to the protocol-specified glucocorticoid taper (Table S2). Multiplicity-controlled secondary end points included sustained complete remission (sustained remission with normalization of the ESR and the CRP level from week 12 through week 52), disease flare–related end points, cumulative exposure to glucocorticoids, glucocorticoid-related adverse events, and patient-reported outcomes, including scores on the Functional Assessment of Chronic Illness Therapy–Fatigue, the Physical Component Summary of the 36-item Short-Form Health Survey, and the Treatment Satisfaction Questionnaire for Medication patient global satisfaction subscale (Table S3).

Investigators who were unaware of the trial group assignments conducted clinical evaluations, reported adverse events, and reviewed laboratory results. Adverse events that emerged during treatment were defined as any event that began or worsened in severity after initiation of upadacitinib or placebo through 30 days after the last dose was received; events were categorized with the use of the *Medical Dictionary for Regulatory Activities*, version 26.1. Laboratory abnormalities were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and adverse events were graded according to version 5.0. An independent cardiovascular adjudication committee evaluated deaths and cardiovascular and thrombotic events according to prespecified criteria.

STATISTICAL ANALYSIS

Efficacy and safety outcomes are shown through week 52 for all patients who underwent randomization and received at least one dose of upadacitinib or placebo. The trial was powered to test for superiority. An overall sample size of 420 was planned to provide at least 90% power to detect an absolute difference of 20 percentage points between the 15-mg upadacitinib group and the placebo group in sustained remission at week 52, at a two-sided alpha level of 0.05. The overall type I error rate of the primary and secondary end points was controlled for multiplicity at the 0.05 level with the use of a graphical multiplicity-adjustment method (Section S3). We began the hierarchical multiplicity-control approach by testing the primary end point in the 15-mg upadacitinib group using an alpha of 0.05, followed by sequentially testing the first seven multiplicity-controlled secondary end points using a prespecified alpha transfer path. To test the results in the 7.5-mg upadacitinib group before completing all end-point analyses for the 15-mg group, the alpha was divided to assess the results for the primary end point in the 7.5-mg group and a group of four end points in the 15-mg group. We used the Cochran–Mantel–Haenszel test with the nonresponder imputation approach (incorporating multiple imputation) to analyze categorical remission–related end points. Continuous end points were calculated with the use of a mixed-effects model for repeated measures, except for cumulative glucocorticoid exposure, which was assessed with the use of the van Elteren test. The time to the first flare of giant-cell arteritis was analyzed with the Kaplan–Meier method. Count-based end points were compared between the upadacitinib groups and the placebo group with the use of Poisson regression models. Post hoc analyses were conducted to evaluate the cumulative glucocorticoid dose administered above the amount expected with the prespecified glucocorticoid taper through 52 weeks. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. Safety data were summarized descriptively. Additional details on statistical methods are provided in Section S4.

RESULTS

PATIENTS

A total of 428 patients underwent randomization and treatment; 209 patients received upadacitinib at a dose of 15 mg, 107 received upadacitinib at a dose of 7.5 mg, and 112 received placebo. A total

of 299 patients (69.9%) completed the upadacitinib or placebo regimen through week 52 (Fig. S2). Demographic and baseline clinical characteristics were balanced across trial groups, with approximately 70% of patients having new-onset giant-cell arteritis and 30% having relapsing disease (Table 1). All the patients underwent temporal-artery biopsy, which revealed features consistent with giant-cell arteritis, had evidence of large-vessel vasculitis on imaging, or both. A total of 40 patients (9.3%) had unequivocal symptoms of polymyalgia rheumatica without cranial symptoms of giant-cell arteritis, although none were enrolled solely on the basis of these symptoms. Most of the patients were women, were 65 years of age or older, and had not previously received

Table 1. Baseline Demographics and Disease Characteristics of the Patients.*

Characteristic	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
Female sex — no. (%)	77 (68.8)	80 (74.8)	156 (74.6)
Age — yr	71.6±7.3	71.1±7.6	70.8±7.3
Age group — no. (%)			
<65 yr	17 (15.2)	19 (17.8)	42 (20.1)
≥65 to <75 yr	59 (52.7)	49 (45.8)	102 (48.8)
≥75 yr	36 (32.1)	39 (36.4)	65 (31.1)
Body-mass index†	25.8±4.3	25.2±5.1	25.3±4.6
Race or ethnic group — no. (%)‡			
Asian	6 (5.4)	6 (5.6)	10 (4.8)
Black or African American	2 (1.8)	1 (0.9)	0
Native Hawaiian or other Pacific Islander	0	1 (0.9)	0
White	103 (92.0)	99 (92.5)	199 (95.2)
Multiple races or ethnic groups	1 (0.9)	0	0
Disease status — no. (%)			
New-onset giant-cell arteritis	76 (67.9)	75 (70.1)	148 (70.8)
Relapsing giant-cell arteritis	36 (32.1)	32 (29.9)	61 (29.2)
Duration of new-onset giant-cell arteritis — days			
Mean	38.2±14.8	35.7±11.1	39.5±28.1
Median	37.0	35.0	36.0
Duration of relapsing giant-cell arteritis — days			
Mean	665.7±816.3	999.2±1179.0	664.9±687.5
Median	277.0	539.5	343.0
Glucocorticoid dose — mg	34.6±11.9	34.5±12.5	34.6±12.7
ESR — mm/hr	21.7±25.5	19.9±21.1	19.5±17.5
Median CRP level (range) — mg/dl	0.23 (0.02–5.83)	0.27 (0.02–5.82)	0.24 (0.02–10.10)
Previous use of interleukin-6 inhibitor — no. (%)§	7 (6.2)	7 (6.5)	9 (4.3)
Ischemia-related vision loss — no. (%)¶	22 (19.6)	14 (13.1)	20 (9.6)
History of PMR — no. (%)	69 (61.6)	54 (50.5)	109 (52.2)
History of unequivocal symptoms of PMR without cranial symptoms of giant-cell arteritis — no. (%)	18 (16.1)	7 (6.5)	15 (7.2)

Table 1. (Continued.)

Characteristic	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)
Basis for diagnosis — no. (%)			
History of positive temporal-artery biopsy	44 (39.3)	48 (44.9)	86 (41.1)
Evidence of large-vessel vasculitis on imaging‖	81 (73.0)	83 (77.6)	159 (76.1)
FACIT-Fatigue score**	37.5±11.7	35.6±11.3	36.0±11.2
SF-36 PCS score††	44.9±9.5	44.0±8.5	43.4±9.0

* Plus–minus values are means ±SD. Percentages were calculated on nonmissing values. Additional baseline characteristics, including geographic region and cardiovascular risk factors, can be found in Table S6. ESR data were available for 111 patients in the placebo group, 106 patients in the upadacitinib 7.5-mg group, and 209 patients in the upadacitinib 15-mg group. CRP denotes C-reactive protein as measured with a high-sensitivity assay, ESR erythrocyte sedimentation rate, GC-T glucocorticoid taper, and PMR polymyalgia rheumatica.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 106 patients in the upadacitinib 7.5-mg group and 206 patients in the upadacitinib 15-mg group.

‡ Race and ethnic group were reported by the patients.

§ Patients who had previously received an interleukin-6 inhibitor and had a disease flare during treatment were excluded from the trial.

¶ This measurement was established before baseline.

‖ Across the groups, the overall distribution of imaging among patients who had received a diagnosis by means of angiography or cross-sectional imaging methods was as follows: ultrasonography, 54.5%; positron emission tomography, 48.6%; computed tomography, 18.3%; magnetic resonance imaging, 13.6%; and angiography, 3.4%. Data were not available for one patient in the placebo group.

** The Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale ranges from 0 to 52, with higher scores indicating less fatigue. Data were available for 108 patients in the placebo group, 103 patients in the upadacitinib 7.5-mg group, and 200 patients in the upadacitinib 15-mg group.

†† The Physical Component Summary of the 36-item Short-Form Health Survey (SF-36 PCS) scores range from 0 to 100, with higher scores indicating better overall health. Data were available for 108 patients in the placebo group, 103 patients in the upadacitinib 7.5-mg group, and 201 patients in the upadacitinib 15-mg group.

interleukin-6 inhibitors. The mean glucocorticoid dose at baseline was 35 mg per day across the groups.

The percentage of the patients who prematurely discontinued upadacitinib or placebo was higher in the placebo group (36.6%) than in the 7.5-mg upadacitinib group (31.8%) and the 15-mg group (25.8%) (Fig. S2). A higher percentage of patients receiving placebo than upadacitinib at a dose of 7.5 mg or 15 mg discontinued upadacitinib or placebo because of adverse events (20.5% vs. 16.8% and 15.3%, respectively) or because of a lack of efficacy (7.1% vs. 3.7% and 3.3%).

EFFICACY

A sustained remission at week 52 was observed in a significantly higher percentage of patients who received upadacitinib at a dose of 15 mg with a 26-week glucocorticoid taper than in those who received placebo with a 52-week glucocorticoid taper (46.4% vs. 29.0%; P=0.002) (Table 2). The 7.5-mg dose of upadacitinib did not lead to a significantly higher percentage of patients with a sustained remission than placebo (41.1% vs. 29.0%). For the secondary end point of sustained complete remission at week 52, upadacitinib at a dose of 15 mg showed a significantly greater treatment effect than placebo, with sustained complete remission observed in 37.1% of the patients in the 15-mg upadacitinib group as compared with 16.1% of patients in the placebo group (P<0.001). Results for each component of sustained complete remission were consistent with the results for the composite end point (Fig. S3). Across nearly all evaluated subgroups, including those defined according to age, sex, new-onset or relapsing giant-cell arteritis, and baseline glucocorticoid dose, treatment with upadacitinib at a dose of 15 mg generally resulted in efficacy consistent with that observed in the overall trial population (Fig. S4).

The total cumulative exposure to glucocorticoids over the course of 52 weeks was significantly lower with upadacitinib at a dose of 15 mg than with placebo (median exposure, 1615 mg vs. 2882 mg; P<0.001) (Table 2). In post hoc analyses of data from patients who completed the trial through week 52, the median cumulative additional glucocorticoid dose received beyond the prespecified taper was 20.0 mg (95% confidence

Table 2. Primary and Secondary End Points through Week 52.*

End Points	Placebo + 52-week GC-T (N=112)	Upadacitinib 7.5 mg + 26-week GC-T (N=107)	Upadacitinib 15 mg + 26-week GC-T (N=209)	Treatment Effect, Upadacitinib 7.5 mg (95% CI)	Treatment Effect, Upadacitinib 15 mg (95% CI)	P Value for Treatment Effect, Upadacitinib 15 mg
Primary end point						
Sustained remission at week 52 — no. (% [95% CI])	33 (29.0 [20.6 to 37.5])	44 (41.1 [31.8 to 50.4])	97 (46.4 [39.6 to 53.2])	12.1 (–0.4 to 24.6)	17.1 (6.3 to 27.8)	0.002
Secondary end points						
Sustained complete remission at week 52 — no. (% [95% CI])	18 (16.1 [9.3 to 22.9])	28 (26.2 [17.8 to 34.5])	78 (37.1 [30.5 to 43.7])	9.9 (–0.8 to 20.6)	20.7 (11.3 to 30.2)	<0.001
Median cumulative glucocorticoid exposure through week 52 (95% CI) — mg†	2882 (2762 to 3253)	1905 (1615 to 2265)	1615 (1615 to 1635)	–1206 (–1452 to –802)	–1267 (–1587 to –1133)	<0.001
Median time to first disease flare through week 52 (95% CI) — days‡	323 (249 to >365)	>365 (316 to >365)	>365	0.75 (0.50 to 1.14)	0.57 (0.40 to 0.83)	0.003
≥1 disease flare through week 52 (95% CI) — %§	55.6 (42.9 to 69.2)	41.3 (32.2 to 51.7)	34.3 (27.4 to 42.4)	0.60 (0.35 to 1.03)	0.47 (0.29 to 0.74)	0.001
Complete remission at week 52 — no. (% [95% CI])	22 (19.6 [12.3 to 27.0])	46 (43.0 [33.6 to 52.4])	105 (50.2 [43.4 to 57.1])	23.5 (11.7 to 35.3)	30.3 (20.4 to 40.2)	<0.001
Complete remission at week 24 — no. (% [95% CI])	40 (36.1 [27.2 to 45.1])	42 (39.3 [30.0 to 48.5])	120 (57.2 [50.5 to 64.0])	3.2 (–9.6 to 16.0)	20.8 (9.7 to 31.9)	<0.001
LS mean change from baseline in SF-36 PCS score at week 52 (95% CI)¶	–1.3 (–3.3 to 0.7)	1.3 (–0.7 to 3.3)	2.5 (1.2 to 3.8)	2.6 (–0.2 to 5.4)	3.8 (1.4 to 6.1)	0.002
Mean no. of disease flares through week 52 per patient-year (95% CI)‖	0.7 (0.5 to 0.9)	0.6 (0.4 to 0.7)	0.4 (0.3 to 0.5)	0.8 (0.6 to 1.2)	0.6 (0.4 to 0.8)	0.001
LS mean change from baseline in FACIT-Fatigue score at week 52 (95% CI)**	–2.4 (–4.7 to –0.1)	1.1 (–1.2 to 3.4)	1.7 (0.2 to 3.1)	3.5 (0.3 to 6.7)	4.0 (1.3 to 6.8)	0.004
LS mean TSQM score at week 52 (95% CI)††	68.8 (63.8 to 73.9)	74.3 (69.4 to 79.1)	71.6 (68.3 to 74.8)	5.4 (–1.4 to 12.3)	2.7 (–3.1 to 8.6)	
Mean no. of glucocorticoid-related adverse events through week 52 per patient-year (95% CI)	1.7 (1.3 to 2.3)	1.7 (1.2 to 2.2)	2.0 (1.7 to 2.4)	0.9 (0.6 to 1.4)	1.1 (0.8 to 1.6)‖	

* The treatment effect is shown as the percentage-point difference between the groups along with the 95% confidence interval (CI) unless otherwise noted. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. The percentages of patients were calculated with the use of a model that incorporated a multiple imputation approach for data that were missing because of logistic restrictions caused by Covid-19 or data after a patient received more than 100 mg of systemic glucocorticoids (prednisone or equivalent) for a non–giant-cell arteritis indication. Response rates were combined from 30 imputed datasets, and the number of responders was calculated on the basis of the response rate for each group. The last four end points were tested together with the use of the Hochberg method at the given significance level (alpha of 0.05; see Section S3). The numbers of patients with missing data are shown in Table S7. Sensitivity analyses for handling missing data under the assumption that the data were not missing at random were conducted with the use of prespecified tipping-point analyses for the secondary end points of cumulative glucocorticoid exposure, percentage of patients with at least one disease flare, SF-36 PCS score, and FACIT-Fatigue score (Section S6 and Tables S8 through S11).

† Data were available for 90 patients in the placebo group, 86 patients in the upadacitinib 7.5-mg group, and 180 patients in the upadacitinib 15-mg group. The median of differences in ranked pairs between the upadacitinib and placebo groups is shown, with negative values favoring upadacitinib.

‡ Values indicated as more than 365 days could not be estimated within the first 52-week treatment period. The end point "at least 1 disease flare through week 52," which was calculated with the use of estimates from the analysis of the end point "time to first disease flare through week 52" as (percentage of patients with ≥1 disease flare at week 52) = 1 – (survival probability/percentage of patients without a disease flare at week 52), provides a landmark measure of survival probability at week 52. The treatment effect is shown as the hazard ratio for disease flare.

§ The treatment effect is shown as the odds ratio.

¶ The treatment effect is shown as the difference in the least-squares (LS) means. Data were available for 44 patients in the placebo group, 49 patients in the upadacitinib 7.5-mg group, and 123 patients in the upadacitinib 15-mg group.

‖ The treatment effect is shown as the rate ratio.

** The treatment effect is shown as the difference in the least-squares means. Data were available for 45 patients in the placebo group, 49 patients in the upadacitinib 7.5-mg group, and 123 patients in the upadacitinib 15-mg group.

†† Scores on the Treatment Satisfaction Questionnaire for Medication (TSQM) patient global satisfaction subscale range from 0 to 100, with higher scores indicating greater satisfaction. The treatment effect is shown as the difference in the least-squares means. Data were available for 45 patients in the placebo group, 52 patients in the upadacitinib 7.5-mg group, and 126 patients in the upadacitinib 15-mg group.

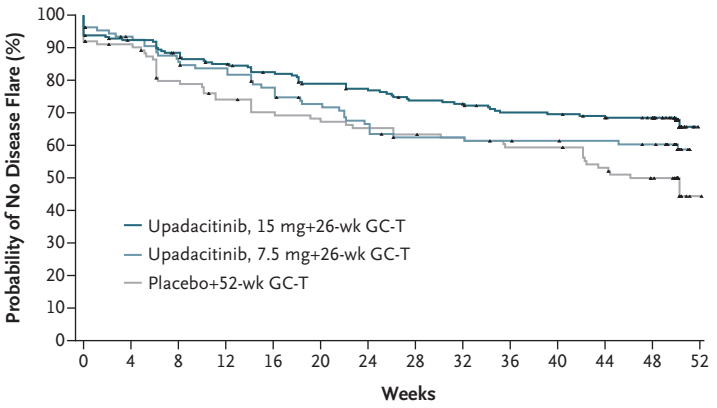
interval [CI], 0 to 40.0) in the 15-mg upadacitinib group and 512.5 mg (95% CI, 35.0 to 1109.0) in the placebo group. Treatment with upadacitinib at a dose of 15 mg resulted in a lower risk of a disease flare through week 52 than placebo (Fig. 1), and fewer patients in the 15-mg upadacitinib group had at least one disease flare (34.3% vs. 55.6%; P=0.001) (Table 2). At week 52, a significantly higher percentage of patients had complete remission without the use of glucocorticoids (after completing the glucocorticoid taper) in the 15-mg upadacitinib group than in the placebo group (50.2% vs. 19.6%; P<0.001).

Treatment with upadacitinib at a dose of 15 mg led to a significantly greater reduction from baseline in fatigue and improvement from baseline in quality of life through week 52 than placebo (Table 2). The results of the comparison between upadacitinib at a dose of 15 mg and placebo in the score on the Treatment Satisfaction Questionnaire for Medication patient global satisfaction subscale at week 52 and in the exposure-adjusted event rates (i.e., events per 100 patient-years) of glucocorticoid-related adverse events through week 52 were not significant. Further comparisons of upadacitinib at a dose of 7.5 mg and placebo for other secondary end points are shown in Table 2, but they were not tested for statistical significance because of the hierarchical approach to controlling for the type I error (Fig. S5).

SAFETY

Safety outcomes over the course of 52 weeks were generally similar in the upadacitinib groups and the placebo group (Table 3). Common adverse events that emerged during treatment in the patients receiving upadacitinib at a dose of 15 mg included headache (16.3%), arthralgia (13.9%), hypertension (13.4%), and coronavirus disease 2019 (Covid-19; 13.4%) (Table S4).

The incidence of adverse events leading to discontinuation of upadacitinib or placebo was lower with upadacitinib than with placebo. The incidence of serious infections was higher with placebo than with upadacitinib. A higher incidence of creatine kinase elevation and of herpes zoster was observed with upadacitinib at a dose of 15 mg than with placebo or upadacitinib at a dose of 7.5 mg. Two cases of serious herpes zoster ophthalmicus were reported in patients who received upadacitinib at a dose of 15 mg.



No. at Risk														Median Time to Disease Flare (95% CI)	Hazard Ratio for Disease Flare (95% CI)	P Value
														wk		
Upadacitinib, 15 mg +26-wk GC-T	209	190	180	171	163	154	150	142	140	132	131	128	123	NE (NE–NE)	0.57 (0.40–0.83)	0.003
Upadacitinib, 7.5 mg +26-wk GC-T	107	96	89	85	78	71	65	59	59	58	57	56	54	NE (45.1–NE)	0.75 (0.50–1.14)	
Placebo+52-wk GC-T	112	98	84	77	72	70	67	65	63	59	59	51	45	46.1 (35.6–NE)	Reference	

Figure 1. Time to First Flare of Giant-Cell Arteritis through Week 52.

The time to the first disease flare was calculated from the time at which the patients had met three criteria in an assessment: the absence of the signs and symptoms of giant-cell arteritis, normalization of the erythrocyte sedimentation rate, and no increase in the glucocorticoid dose. The Kaplan–Meier curve represents the time in the trial and not the visit schedule. A vertical drop in the curves represents a disease flare, and the black triangles represent censored data. Data from patients who never had a disease flare were censored at the last assessment up to week 52, which is indicated in the graph as the clustering of triangles toward the end of the curve. Hazard ratios were estimated with the use of the Cox proportional-hazards model. The P value was calculated with the use of the log-rank test for upadacitinib at a dose of 15 mg as compared with placebo. Testing of upadacitinib at a dose of 7.5 mg as compared with placebo was not conducted because of the hierarchical approach to control for the type I error rate. GC-T denotes glucocorticoid taper, and NE could not be estimated.

Two adjudicated major adverse cardiovascular events occurred in the placebo group; no major adverse cardiovascular events were reported in either upadacitinib group. The incidence of adjudicated venous thromboembolism was similar in all the groups. The incidence of nonmelanoma skin cancer was similar in the 15-mg upadacitinib and placebo groups and lower in the 7.5-mg upadacitinib group. The incidence of other cancers, excluding nonmelanoma skin cancer, was similar in the 15-mg upadacitinib and placebo groups, with none reported in the 7.5-mg upadacitinib group. No active tuberculosis, lymphoma, or gastrointestinal perforations were reported.

Four deaths occurred during the period after initiation of upadacitinib or placebo through 30 days after the last dose was received: two in the placebo group and two in the 15-mg upadacitinib group. In the 15-mg upadacitinib group, one death was attributed to Covid-19 and the other death was adjudicated as an unexplained cause (no autopsy was performed). In addition, a death from a stroke occurred after the completion of this period (by definition, occurring >30 days after the last dose) in a patient who received upadacitinib at a dose of 15 mg, with the last dose administered 60 days before the death occurred (for details, see Section S5).

DISCUSSION

In this phase 3 trial of a treatment for giant-cell arteritis, upadacitinib at a dose of 15 mg once daily in combination with a 26-week glucocorticoid taper showed superior glucocorticoid-free remission and fewer disease flares than placebo with a 52-week glucocorticoid taper. Nearly half the patients (46%) receiving upadacitinib at a dose of 15 mg had a sustained remission at week 52,

Table 3. Safety during the 52-Week Treatment Period.*

Adverse Events	Placebo + 52-week GC-T (N = 112)	Upadacitinib 7.5 mg + 26-week GC-T (N = 107)	Upadacitinib 15 mg + 26-week GC-T (N = 209)
		number (percent)	
Any adverse event†	105 (93.8)	101 (94.4)	200 (95.7)
Serious adverse events†	24 (21.4)	13 (12.1)	47 (22.5)
Adverse events leading to discontinuation of upadacitinib or placebo†	22 (19.6)	17 (15.9)	31 (14.8)
Death‡	2 (1.8)	0	2 (1.0)
Adverse events of special interest			
Serious infection	12 (10.7)	6 (5.6)	12 (5.7)
Opportunistic infection, excluding herpes zoster	1 (0.9)	0	4 (1.9)
Herpes zoster	3 (2.7)	3 (2.8)	11 (5.3)
Cancer, excluding nonmelanoma skin cancer	2 (1.8)	0	4 (1.9)
Nonmelanoma skin cancer	2 (1.8)	1 (0.9)	5 (2.4)
Major adverse cardiovascular events§	2 (1.8)	0	0
Venous thromboembolism¶	4 (3.6)	4 (3.7)	7 (3.3)
Renal dysfunction	3 (2.7)	0	4 (1.9)
Hepatic disorder	5 (4.5)	2 (1.9)	11 (5.3)
Anemia	3 (2.7)	3 (2.8)	14 (6.7)
Neutropenia	1 (0.9)	0	0
Lymphopenia	0	1 (0.9)	3 (1.4)
Creatine kinase elevation	0	0	6 (2.9)
Retinal detachment	3 (2.7)	1 (0.9)	3 (1.4)
Bone fracture	6 (5.4)	6 (5.6)	13 (6.2)

* Shown are the adverse events that emerged during treatment, which are defined as any adverse event with an onset date on or after the first dose of upadacitinib or placebo and no more than 30 days after the last dose. Adverse events of special interest were prespecified in the trial protocol (and were based on upadacitinib findings across all indications and safety concerns reported for other Janus kinase inhibitors). Exposure-adjusted event rates and incidence of adverse events of special interest that emerged during treatment are shown in Figures S6 and S7. No active tuberculosis, lymphoma, or adjudicated gastrointestinal perforation was reported during the treatment period in any group through the data-cutoff date (February 6, 2024).

† This category excludes worsening of giant-cell arteritis as an adverse event; the lack of efficacy is considered separately in the efficacy analyses. Results that include worsening of giant-cell arteritis according to the investigator's judgment as an adverse event in the safety analysis are shown in Table S12.

‡ One death also occurred after the treatment period, 60 days after the last dose of upadacitinib at a dose of 15 mg.

§ These events were adjudicated and include death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke.

¶ These events were adjudicated and include pulmonary embolism and deep-vein thrombosis.

as compared with 29% of the patients receiving placebo. Upadacitinib at a dose of 15 mg also showed superiority over placebo with respect to sustained complete remission, time to a disease flare, cumulative glucocorticoid exposure, fatigue, and quality of life. A significantly higher percentage of patients receiving upadacitinib at a dose of 15 mg than those receiving placebo had

glucocorticoid-free complete remission at week 52 (after completing the glucocorticoid taper before week 52).

Giant-cell arteritis disproportionately affects older adults who have coexisting medical conditions (e.g., hypertension, cardiovascular disease, venous thromboembolism, and diabetes) and who are at high risk for glucocorticoid-related adverse events.[18-21] Upadacitinib, an oral, targeted therapy, would allow for more-rapid glucocorticoid tapering and less cumulative exposure than treatment with glucocorticoids alone. Oral therapies are generally preferred by most patients over injectable options,[22,23] particularly by patients with barriers to injections such as older adults with reduced dexterity or impaired vision.

No new clinically significant safety risks were identified in this older patient population (mean age, 71.1 years) also treated with high doses of glucocorticoids. The incidence of overall adverse events and of serious adverse events over the course of 52 weeks was similar in patients receiving upadacitinib at a dose of 15 mg and in those receiving placebo. The incidence of most adverse events of special interest, including cancer and venous thromboembolism, was generally similar in the upadacitinib groups and the placebo group. Although cardiovascular risk is a potential concern with a JAK inhibitor,[24-26] no major adverse cardiovascular events occurred in the upadacitinib groups during the trial, whereas two major adverse cardiovascular events were reported in the placebo group. However, longer follow-up will be necessary to assess the relative effect on cardiovascular disease risk. The higher dose of upadacitinib was associated with increased risks of herpes zoster and creatine kinase elevation, findings consistent with those in previous studies of JAK inhibitors.[27,28]

This trial had several notable strengths. The placebo-controlled design with a blinded glucocorticoid taper, along with multiplicity-adjusted analyses for secondary end points, added to the rigor of the trial. With more than 400 patients enrolled, the trial included a large sample size for a relatively rare disease. The primary end point, sustained remission, is a standardized clinician-reported outcome used in other trials evaluating giant-cell arteritis. Another strength of the choice of sustained remission as the primary end point was that it does not depend on CRP and ESR normalization, unlike the secondary end point of sustained complete remission, which could have been affected by the ability of upadacitinib to lower CRP and ESR.[29,30] The trial also included patient-reported outcomes covering domains of importance to patients with giant-cell arteritis.[31] Furthermore, the inclusion of patients from 24 countries across four continents enhances the generalizability of the trial results (Table S5).

This trial also had limitations. One limitation was the higher-than-expected percentage of patients who discontinued upadacitinib or placebo — approximately 26% of the patients in the 15-mg upadacitinib group and 37% of the patients in the placebo group. These high percentages could be attributed to the timing of the trial during the Covid-19 pandemic, when older patients were less inclined to leave their homes to visit trial sites, and to the approval of tocilizumab for giant-cell arteritis, which may have led some patients to opt for an already approved therapy. In addition, evaluation of efficacy among the patients for whom interleukin-6 inhibitors were ineffective was not included in this trial. The rates of glucocorticoid-related adverse events should be interpreted with caution because the relatedness to glucocorticoids was determined by the investigator. Future trials might benefit from adjudication or a systematic tool[32] to assess glucocorticoid-related adverse events. Moreover, the short duration of the trial and the potential for increased cardiovascular risk in patients with giant-cell arteritis highlight the need for long-term safety assessments; the extension period of the trial will provide additional data on the safety of upadacitinib in patients with giant-cell arteritis through 2 years.

In this trial involving patients with giant-cell arteritis, upadacitinib at a dose of 15 mg with a 26-week glucocorticoid taper showed efficacy superior to that of placebo with a 52-week glucocorticoid taper, as well as lower glucocorticoid use. The overall safety analyses were consistent with the known safety profile of upadacitinib.[27]

Supported by AbbVie.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in the trial and all the trial investigators for their contributions; Yang Yang, Charles Phillips, and Aditi Kadakia for their contributions to trial design or data analysis; and Matthew Eckwahl and Angela T. Hadsell of AbbVie for medical writing or copy editing assistance with an earlier version of the manuscript.

AUTHOR INFORMATION

[1] Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium; [2] Department of Microbiology, Immunology, and Transplantation, KU Leuven, Leuven, Belgium; [3] AbbVie, North Chicago, IL; [4] Immanuel Krankenhaus Berlin, Medical Center for Rheumatology Berlin–Buch, Berlin; [5] Division of Rheumatology and Immunology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [6] Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark; [7] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [8] University of Western Australia Medical School, Fiona Stanley Hospital, Murdoch, Australia; [9] Division of Hematology and Rheumatology, Tohoku Medical and Pharmaceutical University, Sendai, Japan; [10] St. Joseph's Healthcare, McMaster University, Hamilton, ON, Canada; [11] Department of Rheumatology, Hospital of Brunico, Südtiroler Sanitätsbetrieb — Azienda Sanitaria dell'Alto Adige, Brunico, Italy; [12] Medical University of Graz, Department of Rheumatology, Graz, Austria; [13] Department of Autoimmune Diseases, European Reference Network RITA, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona; [14] Medius Kliniken, Teaching Hospital University of Tübingen, Department of Internal Medicine, Rheumatology, Pneumology, Nephrology and Diabetology, Kirchheim unter Teck, Germany; [15] Division of Rheumatology, Department of Medicine, and the Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia.

REFERENCES

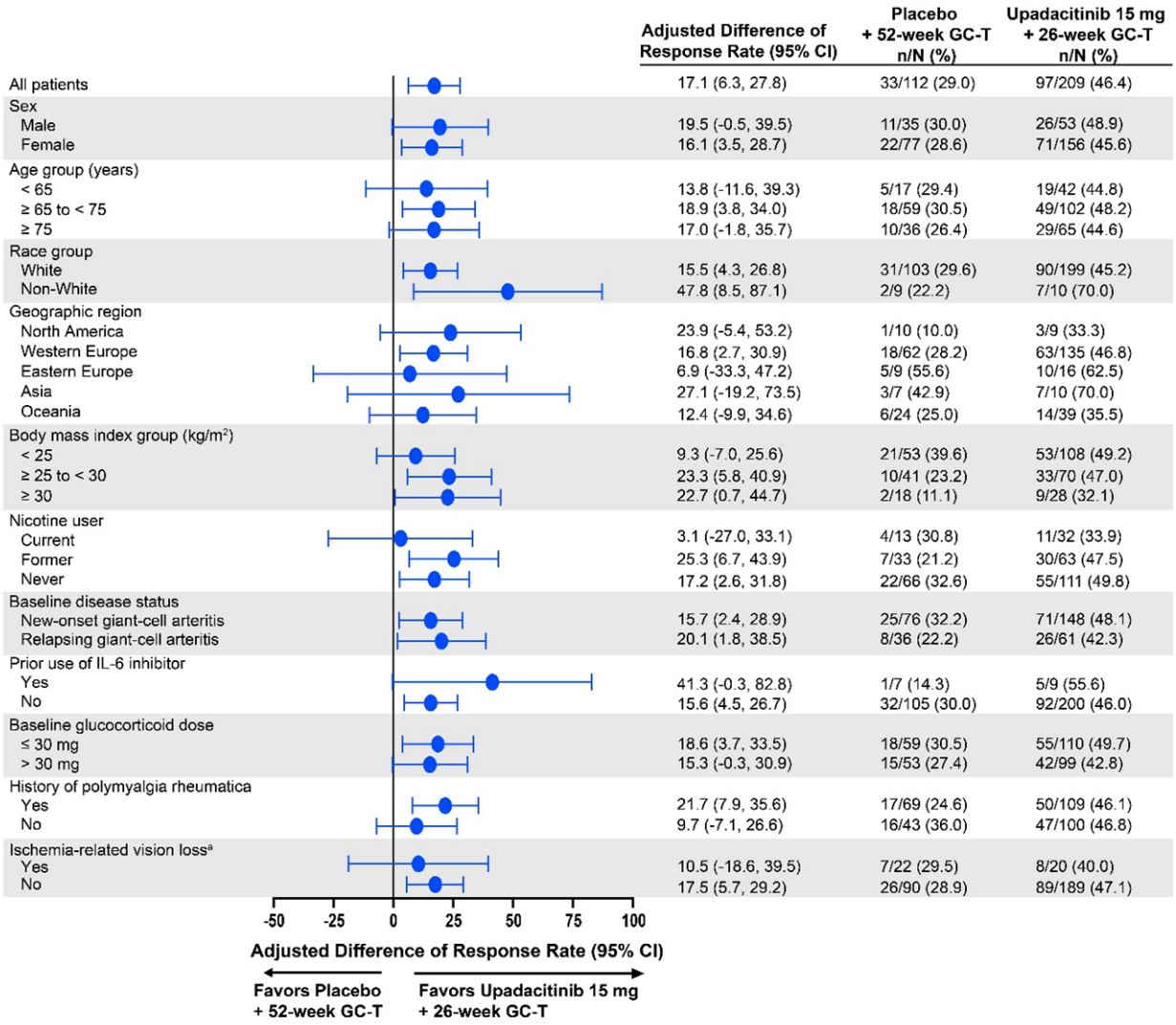
1. Chandran AK, Udayakumar PD, Crowson CS, Warrington KJ, Matteson EL. The incidence of giant cell arteritis in Olmsted County, Minnesota, over a 60-year period 1950-2009. Scand J Rheumatol 2015;44:215-8.
2. Crowson CS, Matteson EL. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. Semin Arthritis Rheum 2017;47:253-6.
3. Li KJ, Semenov D, Turk M, Pope J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. Arthritis Res Ther 2021;23:82.
4. Espígol-Frigolé G, Dejaco C, Mackie SL, Salvarani C, Matteson EL, Cid MC. Polymyalgia rheumatica. Lancet 2023;402:1459-72.
5. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317-28.
6. Alba MA, García-Martínez A, Prieto-González S, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine (Baltimore) 2014;93:194-201.
7. Corbera-Bellalta M, Planas-Rigol E, Lozano E, et al. Blocking interferon γ reduces expression of chemokines CXCL9, CXCL10 and CXCL11 and decreases macrophage infiltration in ex vivo cultured arteries from patients with giant cell arteritis. Ann Rheum Dis 2016;75:1177-86.
8. Hur B, Koster MJ, Jang JS, Weyand CM, Warrington KJ, Sung J. Global transcriptomic profiling identifies differential gene expression signatures between inflammatory and noninflammatory aortic aneurysms. Arthritis Rheumatol 2022;74:1376-86.
9. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). BMC Rheumatol 2018;2:23.
10. Mohamed M-EF, Bhatnagar S, Parmentier JM, Nakasato P, Wung P. Upadacitinib: mechanism of action, clinical, and translational science. Clin Transl Sci 2024;17(1):e13688.
11. Taylor PC, Choy E, Baraliakos X, et al. Differential properties of Janus kinase inhibitors in the treatment of immune-mediated inflammatory diseases. Rheumatology (Oxford) 2024;63:298-308.
12. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2169-81.
13. van der Heijde D, Song I-H, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019;394:2108-17.
14. Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. Lancet 2022;399:2113-28.
15. Sandborn WJ, Feagan BG, Loftus EV Jr, et al. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease. Gastroenterology 2020;158(8):2123-2138.e8.
16. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis 2021;80:312-20.
17. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513-24.
18. Wilson JC, Sarsour K, Collinson N, et al. Serious adverse effects associated with glucocorticoid therapy in patients with giant cell arteritis (GCA): a nested case-control analysis. Semin Arthritis Rheum 2017;46:819-27.
19. Ray JG, Mamdani MM, Geerts WH. Giant cell arteritis and cardiovascular disease in older adults. Heart 2005;91:324-8.
20. Fardet L, Fève B. Systemic glucocorticoid therapy: a review of its metabolic and cardiovascular adverse events. Drugs 2014;74:1731-45.
21. Novikov P, Makarov E, Moiseev S, Meshkov A, Strizhakov L. Venous thromboembolic events in systemic vasculitis. Ann Rheum Dis 2015;74(3):e27.
22. Louder AM, Singh A, Saverno K, et al. Patient preferences regarding rheumatoid arthritis therapies: a conjoint analysis. Am Health Drug Benefits 2016;9:84-93.
23. Myers JT, Dam JV, Imran M, Hashim M, Dhalla AK. Preference for a novel oral alternative to parenterally administered medications. Patient Prefer Adherence 2024;18:1547-62.
24. Fleischmann R, Curtis JR, Charles-Schoeman C, et al. Safety profile of upadacitinib in patients at risk of cardiovascular disease: integrated post hoc analysis of the SELECT phase III rheumatoid arthritis clinical programme. Ann Rheum Dis 2023;82:1130-41.
25. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316-26.
26. Szekanecz Z, Buch MH, Charles-Schoeman C, et al. Efficacy and safety of JAK inhibitors in rheumatoid arthritis:

update for the practising clinician. Nat Rev Rheumatol 2024;20:101-15.
27. Burmester GR, Cohen SB, Winthrop KL, et al. Safety profile of upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. RMD Open 2023;9(1):e002735.
28. Xu Q, He L, Yin Y. Risk of herpes zoster associated with JAK inhibitors in immune-mediated inflammatory diseases: a systematic review and network meta-analysis. Front Pharmacol 2023;14:1241954.
29. Benucci M, Gobbi FL, Fusi P, et al. Different biomarkers of response to treatment with selective Jak-1 inhibitors in rheumatoid arthritis. Front Biosci (Landmark Ed) 2023;28:176.
30. Eriksson P, Skoglund O, Hemgren C, Sjöwall C. Clinical experience and safety of Janus kinase inhibitors in giant cell arteritis: a retrospective case series from Sweden. Front Immunol 2023;14:1187584.
31. Robson JC, Almeida C, Dawson J, et al. Patient perceptions of health-related quality of life in giant cell arteritis: international development of a disease-specific patient-reported outcome measure. Rheumatology (Oxford) 2021;60:4671-80.
32. Miloslavsky EM, Naden RP, Bijlsma JW, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76:543-6.

CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most reports of clinical trials for publication only if the trials have been registered. Current information on requirements and appropriate registries is available at www.icmje.org/about-icmje/faqs/.

Figure S4. Rates of Sustained Remission at Week 52 by Subgroups of Interest in the SELECT-GCA Trial



All subgroups were prespecified for the primary endpoint of sustained remission, except for history of polymyalgia rheumatica, which was evaluated post hoc. Results are based on the Cochran-Mantel-Haensel test. Nonresponder imputation incorporating multiple imputation was used to handle missing data. Response rate, adjusted difference of response rate, and its associated confidence intervals are synthetic results from multiple imputation if there was missing data due to COVID-19 logistical restrictions or data were obtained after a patient received more than 100 mg daily systemic glucocorticoids (prednisone or equivalent) for a non-GCA indication. Confidence interval widths were not adjusted for multiplicity and should not be used in place of hypothesis testing.

[a]Within 8 weeks prior to baseline.

CI, confidence interval; GCA, giant-cell arteritis; GC-T, glucocorticoid taper; IL-6, interleukin-6.