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Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

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ABSTRACT

Objectives Granulocyte-macrophage colony-stimulating factor (GM-CSF) is implicated in pathogenesis of giant cell arteritis. We evaluated the efficacy of the GM-CSF receptor antagonist mavrilimumab in maintaining disease remission.

Methods This phase 2, double-blind, placebo-controlled trial enrolled patients with biopsy-confirmed or imaging-confirmed giant cell arteritis in 50 centres (North America, Europe, Australia). Active disease within 6 weeks of baseline was required for inclusion. Patients in glucocorticoid-induced remission were randomly assigned (3:2 ratio) to mavrilimumab 150 mg or placebo injected subcutaneously every 2 weeks. Both groups received a 26-week prednisone taper. The primary outcome was time to adjudicated flare by week 26. A prespecified secondary efficacy outcome was sustained remission at week 26 by Kaplan-Meier estimation. Safety was also assessed.

Results Of 42 mavrilimumab recipients, flare occurred in 19% (n=8). Of 28 placebo recipients, flare occurred in 46% (n=13). Median time to flare (primary outcome) was 25.1 weeks in the placebo group, but the median was not reached in the mavrilimumab group (HR 0.38; 95% CI 0.15 to 0.92; p=0.026). Sustained remission at week 26 was 83% for mavrilimumab and 50% for placebo recipients (p=0.0038). Adverse events occurred in 78.6% (n=33) of mavrilimumab and 89.3% (n=25) of placebo recipients. No deaths or vision loss occurred in either group.

Conclusions Mavrilimumab plus 26 weeks of prednisone was superior to placebo plus 26 weeks of prednisone for time to flare by week 26 and sustained remission in patients with giant cell arteritis. Longer treatment is needed to determine response durability and quantify the glucocorticoid-sparing potential of mavrilimumab.

Trial registration number ClinicalTrials.gov number: NCT03827018, Europe (EUdraCT number: 2018-001003-36), and Australia (CT-2018-CTN-01865-1).

Key messages

What is already known about this subject?

- Currently available treatments for giant cell arteritis have important limitations. Most patients with giant cell arteritis treated with glucocorticoids alone experience disease relapse and/or develop glucocorticoid-related toxicity, and a significant proportion of patients treated with tocilizumab cannot achieve sustained remission or must discontinue this medication due to adverse events.
- Translational research has implicated granulocyte-macrophage colony-stimulating factor (GM-CSF) in the pathogenesis of giant cell arteritis, with studies showing upregulation of the GM-CSF and TH1/TH17 pathways in temporal arteries of patients with giant cell arteritis and amelioration of the abnormal immune response (eg, inflammatory cell infiltration and expression of interferon-γ and interleukin-6) on GM-CSF signalling blockade with mavrilimumab.

What does this study add?

- This study demonstrated that mavrilimumab in combination with a 26-week prednisone taper was superior to placebo with a 26-week prednisone taper in reducing the risk of flare and maintaining sustained remission and was well tolerated.

How might this impact on clinical practice or future developments?

- The study findings support the hypothesis that GM-CSF signalling activates important pathways in the pathogenesis of giant cell arteritis, and that inhibition of these pathways by GM-CSF receptor blockade with mavrilimumab might maintain remission of the disease.
- These phase 2 results are encouraging for the further development of mavrilimumab as a potential treatment for giant cell arteritis.

INTRODUCTION

Giant cell arteritis (GCA) is the most prevalent form of systemic vasculitis in adults.[1] The disease is driven by $CD4^+$ T-cells (T helper (T_h) 1 and 17 cells) and macrophages that infiltrate large-sized and medium-sized arteries.[2 3] Clinical manifestations include headaches, jaw claudication, ocular ischaemia, polymyalgia rheumatica and constitutional symptoms.[1 4] Possible complications include blindness and aortic aneurysms.[1] Most patients with active GCA exhibit elevated acute-phase reactants, including erythrocyte sedimentation rate (ESR) and serum C reactive protein (CRP) levels,[5] that, along with serial assessment of clinical manifestations, are useful in monitoring disease activity.[1]

Therapeutic options that safely maintain disease remission in patients with GCA are limited.[6] When treated with glucocorticoids alone, approximately 34%–75% of patients experience disease flare on dose reduction or drug discontinuation.[4 7 8] Moreover, the prolonged treatment with glucocorticoids required to control the disease, usually more than 12–18 months, causes significant glucocorticoid-related toxicity in the majority of patients.[9 10] Tocilizumab in combination with ≥6 months of glucocorticoids has demonstrated efficacy in maintaining disease remission and sparing the use of glucocorticoids and is the only approved adjuvant treatment for GCA patients. Unfortunately, 24%–30% of patients receiving tocilizumab flare within 1 year, and approximately 5%–8% of them must discontinue treatment because of side effects.[11 12] Also, given the direct suppression of hepatic acute-phase reactant synthesis, tocilizumab renders ESR and CRP unreliable for monitoring of disease activity and potential intercurrent infectious complications.[13 14] Other medications which have been tried for GCA, such as methotrexate and abatacept, have demonstrated modest benefits at best or need confirmation.[15–17] Therefore, novel treatments that safely maintain remission of GCA while allowing for acute-phase reactant monitoring are needed.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a multifunctional cytokine that modulates the biology of dendritic cells, $CD4^+$ T-cells and macrophages.[18] Preclinical research has implicated GM-CSF in the pathogenesis of GCA.[19–22] GM-CSF, its receptor, and downstream signalling molecules are expressed by immune and endothelial cells in temporal arteries from patients.[19–22] Furthermore, GM-CSF receptor blockade in cultured temporal arteries resulted in decreased expression of dendritic cell, T-cell, and macrophage markers along with down-regulation in transcription of genes associated with the T_h1 and T_h17 immune responses (eg, interferon-γ and interleukin-6).[20 22] In a mouse model of vascular inflammation, GM-CSF inhibition was associated with reduced arterial inflammation and remodelling.[23] Mavrilimumab, an immunoglobulin G4 monoclonal antibody with demonstrated efficacy in phase 2 studies of rheumatoid arthritis,[24 25] blocks GM-CSF signalling by binding to the alpha chain of the receptor.

We conducted a proof-of-concept, randomised, double-blind, placebo-controlled trial to investigate whether mavrilimumab reduced the risk of GCA flare compared with placebo, during a 26-week glucocorticoid taper.

METHODS

Study design

This randomised, double-blind, placebo-controlled phase 2 trial was conducted in 50 centres across 15 countries in North America, Europe, and Australia.

Patients

Patients age 50–85 years with new-onset (diagnosis ≤6 weeks before baseline) or relapsing/refractory (diagnosis >6 weeks before baseline) GCA and active disease within 6 weeks of randomisation were eligible. Active disease was defined as the presence of one or more clinical manifestations, including cranial (eg, headache, scalp or temporal artery tenderness, new/worsening ischaemia-related visual impairment or jaw claudication) or extracranial (eg, new/worsening extremity claudication or polymyalgia rheumatica) signs or symptoms, plus Westergren ESR ≥30 mm per hour or a CRP level ≥1 mg per decilitre. Isolated ESR or CRP elevation was not considered active disease for patient enrolment. GCA diagnosis was confirmed based on a temporal artery biopsy showing GCA features or by findings indicative of vasculitis on temporal artery ultrasonography or large-vessel imaging including magnetic resonance angiography, computed tomography (CT) angiography or positron emission tomography/CT. Complete eligibility criteria are detailed in online supplemental methods.

Procedures

Following a screening period (≤6 weeks), eligible patients were randomly assigned in a 3:2 ratio to mavrilimumab 150 mg or placebo subcutaneously every other week with a 26-week prednisone taper and entered a double-blind, placebo-controlled treatment period (26 weeks), which was followed by a safety follow-up period (12 weeks) (figure 1). Given that in prior 1-year trials with 26-week steroid tapers[11 16] the majority of disease flares occurred within the first 6 months, we limited the treatment period of this proof-of-concept trial to 26 weeks to expedite the generation of efficacy results. Randomisation was stratified by disease type (new onset or relapsing/refractory) at baseline. At baseline, patients were required to be in glucocorticoid-induced remission and on an oral prednisone dose between 20 and 60 mg daily. Remission at baseline was defined as the absence of disease signs and symptoms and ESR<20 mm per hour or serum CRP concentration <1 mg per decilitre. From baseline, the prednisone dose was tapered weekly in both groups as stipulated by the protocol. Additional details can be found in online supplemental file.

Outcomes

Efficacy

Patients were assessed at planned study visits and during unscheduled visits to determine disease remission status and whether the protocol prednisone taper could continue. It was recommended that the investigator evaluate signs and symptoms of GCA before reviewing laboratory or imaging results to minimise potential bias. ESR and/or CRP levels were measured locally. Patients requiring treatment for flare during the double-blind period discontinued study drug and received standard treatment, including glucocorticoids, as per the investigators' clinical judgement. After the 26-week treatment period, patients discontinued study drug and transitioned to standard of care, which could include glucocorticoids, during a 12-week washout period. Patients were closely monitored for safety and flare through week 38.

The primary efficacy end point was time to first GCA flare by week 26. Flare was centrally adjudicated by an independent, blinded clinical end point adjudication committee and defined as elevation of ESR (≥30 mm/hour) and/or CRP (≥1 mg/dL) along with either the presence of unequivocal cranial or extracranial signs or symptoms or the occurrence of new or worsening

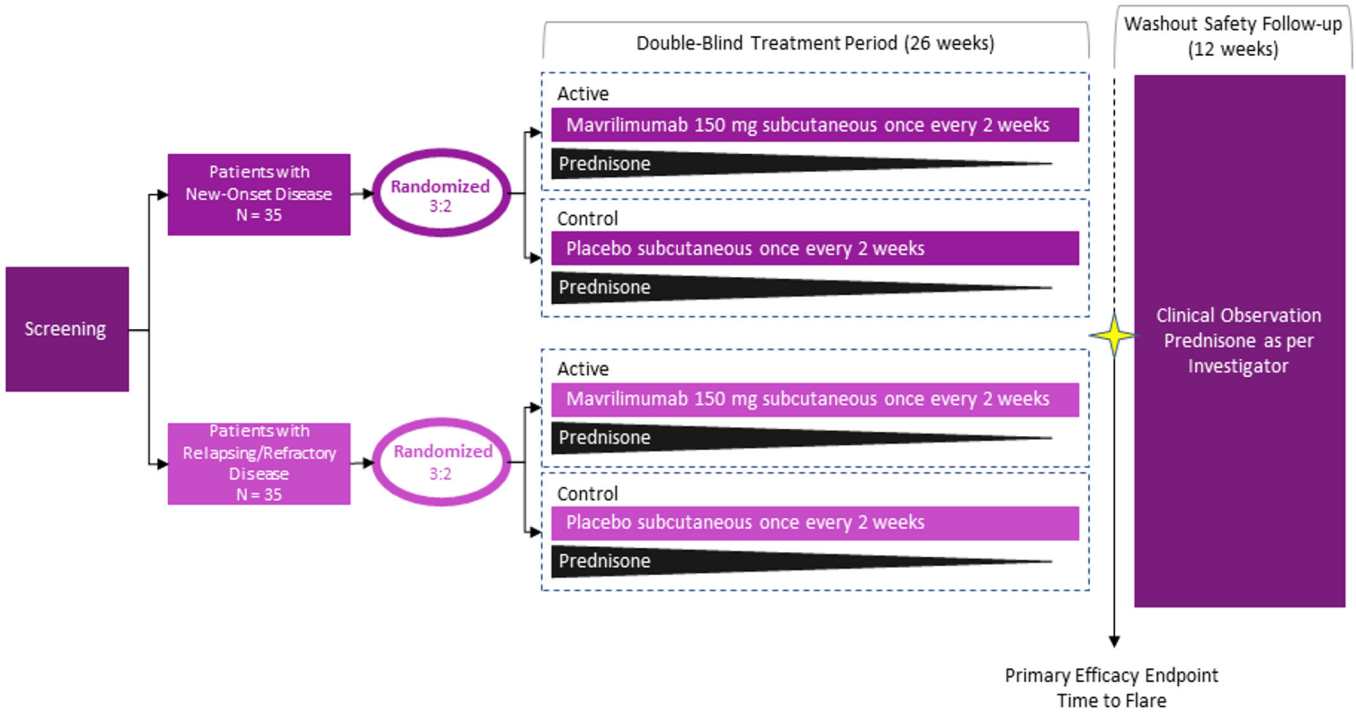

Figure 1 Trial design. Patients were randomised in a 3:2 ratio to mavrilimumab or placebo using disease type (new onset or relapsing/refractory) as a stratification factor. Prednisone was tapered over the 26-week study as specified in the protocol.

imaging abnormalities suggestive of active vasculitis. ESR or CRP elevation was not considered disease flare in the absence of signs, symptoms or imaging abnormalities suggesting disease activity. Further details of flare adjudication are included in online supplemental methods.

A key prespecified secondary efficacy end point was sustained remission rate at week 26 using Kaplan-Meier estimation, which was defined as the absence of flare from randomisation through week 26. Time to flare and sustained remission by week 26 were also assessed in the subgroups of patients with new-onset and relapsing/refractory disease at baseline. Cumulative prednisone dose by treatment arm was assessed. The proportion of patients with elevated ESR or CRP but without giant-cell arteritis flare was assessed in a post hoc analysis. Additional secondary end points and their hierarchy are described in online supplemental methods.

Safety

Safety was assessed through week 38 for all patients who received at least one mavrilimumab or placebo dose. Incidence, severity, and relationship of adverse events to study drug were summarised by treatment group. A data-monitoring committee periodically reviewed all safety data during the trial. Patients underwent serial pulmonary function testing and completed the modified Borg Dyspnoea Scale[26] at regular intervals. An independent committee adjudicated pulmonary adverse events of special interest including the potential occurrence of pulmonary alveolar proteinosis.[27]

Statistical analyses

A sample size of approximately 70 patients was determined based on an assumption, consistent with literature data, that 50% of placebo recipients and 15% of mavrilimumab recipients would flare by week 26, with a median time to flare of approximately 26 weeks in placebo group and 111 weeks in mavrilimumab group, corresponding with an HR of approximately 0.234. Using a time-to-flare model and a 3:2 randomisation ratio, we calculated that 20 flares would give the trial 87% power to detect a significant difference between treatment groups with a two-sided alpha level of 0.05. The analysis of the new onset and relapsing/refractory subgroups, while prespecified, was not powered for significance. The efficacy end point analysis was performed in the modified intention-to-treat population, which included all randomised patients who had received at least one dose of study treatment and had at least one assessment in the double-blind treatment period. The primary end point and other time-to-event end points were summarised with percentiles and 95% CIs using the Kaplan-Meier method. Patients without a flare were censored at the last assessment by week 26 or by end of treatment visit, in case of early treatment discontinuation, for calculation of the time to flare. A log-rank test stratified by disease type (new onset vs relapsing/refractory) at baseline was used to compare mavrilimumab with placebo. The number and percentage of patients who had a flare during the 26-week double-blind period were summarised for each treatment group. A Cox proportional hazards model was used to calculate hazard ratios and 95% CIs. Sustained remission at week 26 was derived by Kaplan-Meier curve analysis.

All secondary outcomes based on proportions were assessed using the Cochran-Mantel-Haenszel test.

A gatekeeping multiplicity-adjustment procedure in combination with the Hochberg method was applied for prespecified stepwise testing of the primary end point and the secondary end points. If the two-sided p value for an end point (highest in hierarchy) was no more than 0.05, the next prespecified end point in the hierarchy would be tested at the same alpha level. Details of hierarchy are provided in online supplemental methods.

RESULTS

Patients

Of 112 patients assessed for eligibility, 70 were enrolled in the trial between 20 September 2018 and 27 January 2020.

Table 1 Baseline characteristics of the intention-to-treat population†

	Mavrilimumab‡ (n=42)	Placebo (n=28)
Age (years)	69.7 (7.0)	69.7 (8.3)
Sex		
Male	10 (24%)	10 (36%)
Female	32 (76%)	18 (64%)
Race		
White	40 (95%)	28 (100%)
Other	2 (5%)	0
Hispanic or Latino ethnicity	1 (2%)	2 (7%)
Weight (kg)	70.9 (18.7)	71.1 (12.0)
Body mass index (kg/m^2)	26.2 (6.8)	26.1 (3.6)
Prior treatment		
Glucocorticoids	42 (100%)	27 (96%)
Methotrexate	0	1 (4%)
Diagnostic confirmation		
By positive temporal artery biopsy	22 (52%)	9 (32%)
By positive imaging	29 (69%)	22 (79%)
Time since diagnosis (months)	7.9 (15.4)	9.8 (21.8)
Giant-cell arteritis		
New onset*	24 (57%)	11 (39%)
Relapsing/refractory*	18 (43%)	17 (61%)
Giant-cell arteritis type		
Cranial signs or symptoms	32 (76%)	21 (75%)
Extracranial signs or symptoms	9 (21%)	6 (21%)
C reactive protein level (study eligibility value) (mg/dL)	4.7 (4.7)	3.6 (3.2)
Erythrocyte sedimentation rate (study eligibility value) (mm/hour)	57.0 (24.6)	55.1 (30.2)
Prednisone starting dose		
≤30 mg	16 (38.1)	14 (50.0)
>30 mg	26 (61.9)	14 (50.0)

Data are n (%) or mean (SD).
*Seven patients were misstratified due to investigator error (new onset vs relapsing/refractory misclassification) at study entry. For the efficacy analysis, these patients were included in the appropriate protocol-defined subgroups, leading to a proportion of 57% of patients with new-onset disease in the mavrilimumab group (43% relapsing/refractory) and 39% of patients with new-onset disease in the placebo group (61% relapsing/refractory).
†Baseline is last assessment within 3 days before the first dose of mavrilimumab or placebo.
‡150 mg subcutaneously every 2 weeks.

Figure 1 shows the clinical trial schema. A total of 42 patients were randomly assigned to mavrilimumab and 28 to placebo. The demographic and baseline characteristics of the treatment groups are displayed in table 1. GCA diagnosis was confirmed by biopsy in 31 (44%) patients and by imaging in 51 (73%) patients. A total of 66 patients completed the 26-week study period (figure 2).

Primary and key secondary efficacy outcomes

During the 26-week placebo-controlled period, 21 patients developed an adjudicated flare: eight (19%) mavrilimumab recipients and 13 (46.4%) placebo recipients. GCA signs or symptoms were present in 20 of the 21 patients with flare; in the one other patient, flare was determined based on presence of active vasculitis on ultrasound imaging. Median time to flare (primary end point) in placebo recipients was 25.1 weeks (95% CI 16.0 to not estimable (NE)). The median time to flare among mavrilimumab recipients was not reached within the 26-week follow-up period. Mavrilimumab reduced the risk of flare vs placebo (HR, 0.38; 95% CI 0.15 to 0.92; p=0.026) (figure 3). Sustained remission at week 26 (key secondary end point) was reached in 83.2% of mavrilimumab recipients and 49.9% of placebo recipients (33.3 percentage points difference; p=0.0038) (figure 4, table 2). Detailed flare information is provided in online supplemental table S1.

New-onset and relapsing/refractory disease

Among the subgroup of patients with new-onset GCA at baseline, flare occurred in 12.5% of mavrilimumab recipients and 36.4% of placebo recipients (HR, 0.29; 95% CI, 0.06 to 1.31) (table 2; online supplemental figure S1A); 91.3% of mavrilimumab recipients and 62.3% of placebo recipients had sustained remission at week 26 (table 2, online supplemental figure S2A). Among the subgroup of patients with relapsing/refractory disease at baseline, flares occurred in 27.8% of mavrilimumab recipients and 52.9% of placebo recipients (HR, 0.43; 95% CI 0.14 to 1.30) (table 2; online supplemental figure S1B); sustained remission at week 26 was observed in 72.2% of mavrilimumab recipients and 41.7% of placebo recipients (table 2, online supplemental figure S2B).

Cumulative prednisone dose

The mean cumulative prednisone dose by week 26 was 2074 mg in mavrilimumab recipients and 2403 mg in placebo recipients (nominal p=0.067); least-squares mean difference (nominal 95% CI) was –326 mg (–676 mg to 23 mg). Additional secondary end points assessed at week 26 are reported in table 3 and the online supplemental results.

Acute-phase reactants

Among the 21 patients who had a flare, all had increased ESR or CRP values at the time of flare (by pre-specified flare definition); the median (IQR) CRP level was 1.8 (1.4–6.3) mg per decilitre in mavrilimumab recipients and 1.8 (1.2–2.8) mg per decilitre in placebo recipients. Corresponding ESR values were 40 (33 –73) mm per hour in mavrilimumab recipients and 49 (33–51) mm per hour in placebo recipients (online supplemental table S2). Among 34 mavrilimumab recipients who did not have a flare, 47.1% had at least one elevated ESR (≥30 mm/hour) and 29.4% had at least one elevated CRP (≥1 mg/dL) value through week 26. Among 15 placebo recipients who did not have a flare, 66.7% had at least one elevated ESR and 73.3% had at least one elevated CRP value through week 26 (online supplemental table S2).

Safety

Adverse events were reported in 78.6% of mavrilimumab recipients and 89.3% of placebo recipients (table 4). Serious adverse events, all unrelated to study drug, were reported in 4.8% of mavrilimumab recipients (one case each of hypertrophic cardiomyopathy and dementia) and 10.7% of placebo recipients (one case each of gastrointestinal haemorrhage, peripheral oedema and pulmonary fibrosis). No adverse event resulted in permanent vision loss or death in either treatment group. Adverse events leading to study drug discontinuation occurred in one patient in each treatment group: dementia in a mavrilimumab recipient and chest pain in a placebo recipient.

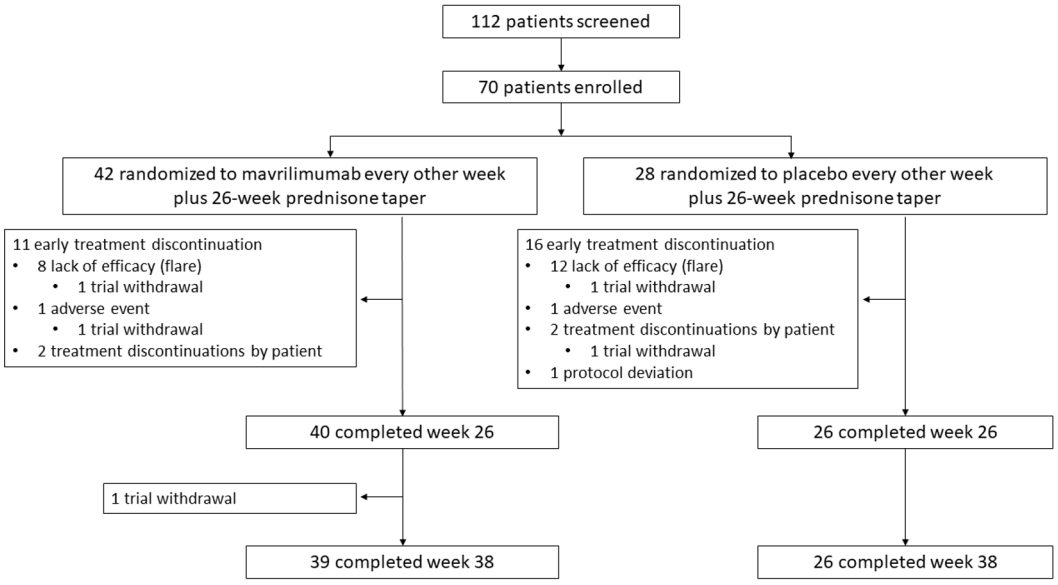

Figure 2 Trial profile. Not all patients who discontinued treatment withdrew from the trial; two patients receiving mavrilimumab and two patients receiving placebo withdrew before week 26, and one patient receiving mavrilimumab withdrew between week 26 and week 38.

The most frequent non-serious adverse events in mavrilimumab recipients were non-specific headache, nasopharyngitis and neck pain. Infections were reported in 42.9% of mavrilimumab recipients and 35.7% of placebo recipients. No serious or severe infections occurred during the trial. Respiratory adverse events were reported in similar proportions in the treatment groups (mavrilimumab, 11.9%; placebo, 10.7%). In mavrilimumab recipients, these included mild cough, mild dyspnoea and mild vasomotor rhinitis. There were no substantive differences between treatment groups in pulmonary function tests, including diffusing capacity of the lung for carbon monoxide, and no cases of pulmonary alveolar proteinosis occurred.

DISCUSSION

This trial provides the first evidence of the efficacy and safety of mavrilimumab in patients with GCA. Mavrilimumab with a 26-week prednisone taper was superior to placebo with a 26-week prednisone taper in reducing the risk of flare and maintaining sustained remission. Consistent efficacy trends were observed in new-onset and relapsing/refractory disease subgroups, although this analysis was not powered for statistical significance. Mavrilimumab was well tolerated, and the overall incidence of adverse events and serious adverse events was similar between groups.

GCA treatments that safely maintain disease remission are lacking.[6] The clinical course of patients treated exclusively with

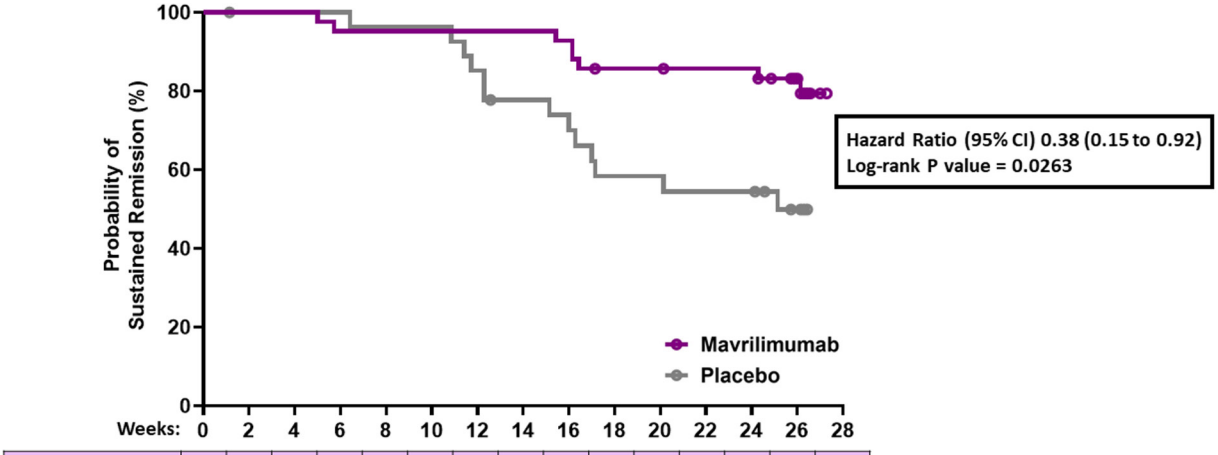

Figure 3 Time to first flare of giant-cell arteritis in all patients. At baseline, patients had to be in remission (defined as the absence of giant-cell arteritis signs and symptoms and erythrocyte sedimentation rate <20 mm/hour or C reactive protein level <1 mg/dL) and receiving an oral prednisone dose between 20 mg and 60 mg daily. Patients who discontinued treatment for reasons other than flare were censored for the calculation of time to flare. The median time to flare could not be calculated for patients receiving mavrilimumab because fewer than 50% of patients experienced a flare during the 26 weeks study period.

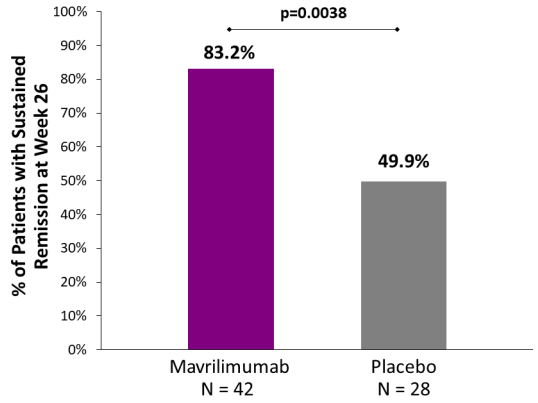

Figure 4 Sustained remission rate of giant-cell arteritis in all patients at week 26. The difference in sustained remission at week 26 (key secondary endpoint) was statistically significant (33.3 percentage points; p=0.0038). Sustained remission was defined as the absence of flare from randomisation through week 26. Sustained remission rate was derived by Kaplan-Meier curve analysis.

glucocorticoids is complicated by high rates of disease flare and increased incidence of glucocorticoid-related toxicity.[4 7 8] Tocilizumab is the only GCA medication with confirmed, clinically meaningful efficacy in terms of remission maintenance and glucocorticoid-sparing.[11] However, 24%–30% of patients receiving tocilizumab flare within 1 year, and approximately 5%–8% of them must discontinue treatment because of side effects.[11–13] In this study, mavrilimumab reduced the risk of flare without adverse events of serious infection or pulmonary alveolar proteinosis,[28] becoming a promising option for further development in a field in which alternative treatments are a great unmet need.

It is well recognised that the elevation of ESR or serum CRP is not completely sensitive or specific for the diagnosis of GCA flare.[5 13] However, these acute-phase reactants have been widely used by clinicians as one of several practical elements for monitoring disease activity status in steroid-treated patients. Because tocilizumab reduces IL-6 activity in the liver, it directly inhibits hepatic synthesis of acute-phase reactants and reduces ESR and CRP independently of its immunomodulatory action,[13] rendering these biomarkers unreliable for monitoring disease activity.[13] The fact that flares in this trial were associated with increased acute-phase reactants regardless of whether patients were on mavrilimumab or only glucocorticoids suggests that ESR and CRP retained their clinical diagnostic value during GM-CSF blockade.

The safety profile of mavrilimumab was consistent with that observed in larger, long-term studies of patients with rheumatoid arthritis.[25 29] In this phase 2 trial, mavrilimumab was well tolerated, and most adverse events were mild or moderate. Because GM-CSF plays an important role in lung homeostasis by promoting alveolar macrophage-induced surfactant clearance,[27 28] respiratory adverse events, including changes in lung function, were assessed by an independent pulmonary evaluation committee. Of note, there were no differences in pulmonary function tests between treatment groups and no cases of pulmonary alveolar proteinosis occurred during the trial.

The design of this phase 2 study incorporated strategic development-phase-specific trade-offs in strengths and limitations as well as guidance provided by regulatory agencies during review of the protocol. On the one hand, informed by the timing of disease flare in other trials,[11 16] the proposed 26-week placebo-controlled treatment period allowed for expedited generation of proof-of-concept data. The time-to-event variable of time-to-flare was chosen for the primary end point (as opposed to disease remission at a given timepoint) because it would allow for a more comprehensive interpretation of the results by adding the domain of time and the event cadence to the cumulative crude event rates. On the other hand, a period longer than 26 weeks would have been ideal to properly assess long-term remission maintenance and glucocorticoid sparing, important treatment objectives for this chronic, relapsing disease. In this trial, the mean cumulative prednisone dose was lower in mavrilimumab recipients than in placebo recipients, due to higher disease flare and glucocorticoid rescue rates in patients in the placebo group.

Table 2 Primary end point and key secondary end points

End point	Mavrilimumab**	Placebo	HR or difference	P value*
All study patients†	(N=42)	(N=28)	–	–
Patients with flare	8 (19.0%)	13 (46.4%)	–	–
Time to flare (primary end point)—week	NE (NE, NE)	25.1 (16.0 to NE)	0.38 (0.15 to 0.92)‡	0.026
Sustained remission§—%	83.2 (67.9 to 91.6)	49.9 (29.6 to 67.3)	33.3 (10.7 to 55.8)¶	0.0038
Patients with new-onset† giant-cell arteritis at baseline	(N=24)	(N=11)	–	–
Patients with flare	3 (12.5%)	4 (36.4%)	–	–
Time to flare—week	NE (NE to NE)	NE (11.7 to NE)	0.29 (0.06 to 1.31)‡	–
Sustained remission§—%	91.3 (69.3 to 97.7)	62.3 (27.7 to 84.0)	28.9 (–2.7 to 60.5)¶	–
Patients with relapsing/refractory† giant-cell arteritis at baseline	(N=18)	(N=17)	–	–
Patients with flare	5 (27.8%)	9 (52.9%)	–	–
Time to flare—week	NE (16.4 to NE)	22.6 (16.0 to NE)	0.43 (0.14 to 1.30)‡	–
Sustained remission§—%	72.2 (45.6 to 87.4)	41.7 (17.4 to 64.5)	30.6 (–2.1 to 63.2)¶	–

Data are n (%) or median (95% CI), except as indicated.
*P values are two sided.
†Modified intention-to-treat (mITT) population.
‡Calculated using a Cox proportional hazards model with treatment as covariate.
§The Kaplan-Meier method was used to estimate event rates. In some cases, results were NE because the event rates were too low.
¶Calculated as the difference in sustained remission between the two groups using normal approximation with placebo as the reference.
**150 mg subcutaneously every 2 weeks.
NE, not estimable.

Table 3 Other secondary end points

End point	Mavrilimumab* (N=42)	Placebo (N=28)	P value
Time to elevated erythrocyte sedimentation rate by week 26,† median (95% CI) weeks‡	26.1 (16.1, NE)	12.1 (8.1, 16.6)	0.028§
Time to elevated C reactive protein level by week 26,¶ median (95% CI) weeks‡	NE (8.1, NE)	12.3 (3.3, 24.1)	0.038§
Time to signs and symptoms of giant-cell arteritis or new or worsening vasculitis by imaging by week 26, median (95% CI) weeks‡	NE (NE, NE)	25.1 (15.1, NE)	0.065§
Cumulative prednisone dose at week 26, mean (SD) mg	2074 (708)	2403 (1014)	0.067**
Percentage of patients completing glucocorticoid taper†† and with normal erythrocyte sedimentation rate by week 26	19 (45.2%)	4 (14.3%)	0.020**
Percentage of patients completing glucocorticoid taper†† and with normal C reactive protein level by week 26	10 (23.8%)	4 (14.3%)	0.55**
Percentage of patients completing glucocorticoid taper†† and with no signs or symptoms of giant-cell arteritis by week 26	30 (71.4%)	9 (32.1%)	0.0031**
Cumulative prednisone dose at week 38‡‡, mean (SD) mg	2465 (1107)	2845 (1320)	0.16**

Data are n (%) except as indicated.
*150 mg subcutaneously every 2 weeks.
†Elevated erythrocyte sedimentation rate is defined as the first rate greater than or equal to 30 mm/hour; patients with an elevated rate within 3 days of the first dose of study drug were excluded from the analysis.
‡Kaplan-Meier method.
§Log-rank test stratified by randomisation strata.
¶Elevated C reactive protein level is defined as the first level greater than or equal to 1.0 mg/dL; patients with an elevated level within 3 days of the first dose were excluded from the analysis.
**Analysed by Cochran-Mantel-Haenszel test stratified by randomisation strata. Nominal p value.
††Patients were considered to have completed glucocorticoid taper if by week 26 they were receiving 1 mg/day for patients who had a starting dose of 60 mg/day, or 0 mg/day for patients who had a starting dose of less than 60 mg/day.
‡‡After the 26-week treatment period, investigators could manage disease in patients at their discretion, including use of glucocorticoids.

The difference between groups through week 26, however, did not reach statistical significance, likely because of the late time-to-flare (median 25.1 weeks) in the placebo group relative to the 26-week time point at which the assessment of cumulative prednisone dose ended.

Table 4 Treatment-emergent adverse events

Adverse events	Mavrilimumab* (N=42)	Placebo (N=28)
Patients with ≥1 adverse event	33 (78.6%)	25 (89.3%)
Serious adverse event	2 (4.8%)	3 (10.7%)
Serious adverse event related to study drug	0	0
Adverse event resulting in death	0	0
Adverse event leading to study drug discontinuation	1 (2.4%)	1 (3.6%)
Adverse events by maximum severity†		
Mild	18 (42.9%)	13 (46.4%)
Moderate	14 (33.3%)	11 (39.3%)
Severe	1 (2.4%)	1 (3.6%)
Most common adverse events‡		
Headache	6 (14.3%)	7 (25.0%)
Nasopharyngitis	5 (11.9%)	3 (10.7%)
Neck pain	4 (9.5%)	2 (7.1%)
Arthralgia	2 (4.8%)	4 (14.3%)
Hypertension	1 (2.4%)	4 (14.3%)
Back pain	3 (7.1%)	3 (10.7%)
Muscle spasms	3 (7.1%)	3 (10.7%)
Upper respiratory tract infection	3 (7.1%)	2 (7.1%)
Constipation	3 (7.1%)	0
Diarrhoea	0	3 (10.7%)
Fall	2 (4.8%)	5 (17.9%)

Data are n (%).
*150 mg subcutaneously every 2 weeks.
†Each patient is represented only with maximum severity.
‡Reported in >2 patients in either treatment group.

A slight imbalance in the number of patients with new-onset and relapsing/refractory disease between groups could have influenced the results to some extent and may represent a limitation of the study. Although, such possibility seems unlikely in view of prior research demonstrating that duration of disease and the status of newly diagnosed vs relapsing disease do not independently predict treatment failure,[30] confirmation of these phase 2 results in a larger trial with well-balanced baseline features is required.

Current medications for GCA (eg, glucocorticoids and tocilizumab) target primarily the $CD4^+$ T_h17 immune response, possibly leaving residual $CD4^+$ T_h1 pathway activity, which may explain why a sizeable proportion of patients flare with these treatments. In contrast, GM-CSF blockade with mavrilimumab may address the pathogenic mechanisms of GCA more comprehensively via its demonstrated suppressive effects on macrophages, $CD4^+$ T_h17 cells, and $CD4^+$ T_h1 cells, including downregulation of IFNγ expression.[22 23] However, further mechanistic research linked to clinical outcomes is needed before firm conclusions can be drawn.

In summary, mavrilimumab given with a 26-week prednisone taper significantly reduced the risk of flare and improved the sustained remission rates compared with placebo with a 26-week prednisone taper in patients with GCA. Mavrilimumab was well tolerated, and no new safety signals emerged in this clinical trial. These results are supportive of further clinical development of mavrilimumab; confirmation of these overall results, precise distinction of efficacy in new-onset and relapsing/refractory disease subgroups, and determination of response durability and glucocorticoid-sparing potential should all be addressable in a larger pivotal clinical trial of longer duration.

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Contributors The authors MCC, SHU, and JFP act as guarantors of this work. All authors participated in reviewing and editing the manuscript, data curation and approved the submitted draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors MCC and SHU share first Authorship. The authors MCC, SHU, MS, TZ, LP and JFP accessed and completed formal analysis of all underlying data. The authors MCC, SHU, IPW, LP and JFP participated in conceptualisation. The authors MCC, SHU and JFP supervised the study. The original draft was written by authors MCC and SHU. The sponsor (Kiniksa) participated in trial design and patient recruitment and performed data analysis and interpretation. Kiniksa supported the decision to submit the article for publication.

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Data availability statement Data are available on reasonable request. The individual anonymised data supporting the analyses contained in the manuscript will be made available on reasonable written request from researchers whose proposed use of the data for a specific purpose has been approved. Data will not be provided to requesters with potential or actual conflicts of interest, including individuals requesting access for commercial, competitive or legal purposes. Data access may be precluded for studies in which clinical data were collected subject to legal, contractual or consent provisions that prohibit transfer to third parties. All those receiving access to data will be required to enter into a Data Use Agreement (DUA), which shall contain terms and conditions that are customary for similar agreements and similar companies in the industry. For requests, please email JFP, Kiniksa Pharmaceuticals Chief Medical Officer jpaolini@kiniksa.com.

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Efficacy and safety of mavrilimumab in giant-cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

Online Supplemental Material

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METHODS

Full Inclusion/Exclusion Criteria

Inclusion Criteria

- Able and willing to provide written informed consent and to comply with the study protocol
- Age 50 to 85 years inclusive
- Diagnosis of new-onset or relapsing/refractory giant-cell arteritis (see further details below)
- Remission of giant-cell arteritis at or before day 0 (resolution of giant-cell arteritis symptoms and C-reactive protein [CRP] levels less than 1.0 mg/dL or erythrocyte sedimentation rate [ESR] less than 20 mm in first hour), such that the patient can safely participate in the study and follow the protocol-defined procedures, including initiation of the prednisone taper at the protocol-specified starting dose (i.e., ≤60 mg/day)
- At day 0, receiving or able to receive oral prednisone up to 60 mg/day for the treatment of giant-cell arteritis
- If using methotrexate, oral or parenteral up to 25 mg/wk is permitted in screening if started more than 6 weeks before day 0 and should be tapered to zero by day 0
- Willing to receive antiplatelet therapy, depending on investigator's decision
- Willing to receive treatment for prevention of glucocorticoid-induced osteopenia/osteoporosis, depending on investigator's decision
- Female patients must be:
    - Postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause), or
    - Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or having a male partner with vasectomy as affirmed by the patient, or
    - Nonpregnant, nonlactating, and if sexually active having agreed to use a highly effective method of contraception (i.e., hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from the screening visit until the final washout safety follow-up visit 84 ± 3 days from end-of-treatment visit
- Male patients must have documented vasectomy or if sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (i.e., hormonal contraceptives associated with the inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from day 0 until the final washout safety follow-up visit 84 ± 3 days from end-of-treatment visit. Male patients must agree to refrain from donating sperm during the study period.

Exclusion Criteria

- Major surgery within 8 weeks before screening or planned major surgery within 12 months after randomisation
- Transplanted organs (except corneal transplant performed more than 3 months before randomisation)
- Major ischemic event unrelated to giant-cell arteritis within 12 weeks of screening
- Concurrent enrollment in another clinical study, with the exception of observational studies
- Previous treatment with mavrilimumab
- Treatment with any nonbiologic investigational drug therapy within 4 weeks or 5 half-lives of the study agent, whichever was longer, before screening
- Any cell-depleting biologic therapies (e.g., anti-CD20) within 12 months before day 0; or previous treatment with noncell-depleting biologic therapies (e.g., anti–tumor necrosis factor [TNF], anakinra, anti–interleukin 6 [IL-6] receptor [e.g., tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) before screening
- Treatment with alkylating agents within 12 weeks before screening
- Intramuscular, intra-articular, or intravenous glucocorticoids within 4 weeks before screening
- Receipt of live (attenuated) vaccine within 4 weeks before day 0

- Treatment with hydroxychloroquine, cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil within 4 weeks before screening
- Female patients who are pregnant, intending to become pregnant, or breastfeeding
- Any condition that, in the opinion of the investigator, could interfere with evaluation of mavrilimumab or interpretation of patient safety or confound the results of the study
- Known history of allergy or reaction to any component of the mavrilimumab or placebo formulation or to any other biologic therapy or prednisone or any of its excipients
- Positive (or 2 indeterminate) QuantiFERON test results
- Clinically significant active infection, including signs/symptoms suggestive of infection, any significant recurrent or chronic infection (including positive hepatitis C virus antibody [HCVAb]), or any episode of infection requiring hospitalization or treatment with intravenous antibiotics within 12 weeks before screening; patients with any opportunistic infection within 6 months before screening
- Patients with chronic active hepatitis B infection as defined below will be excluded from the study:
    - Hepatitis B surface antigen (HbsAg) positive
    - Hepatitis B anti-core antibody positive but anti-surface antibody negative
- Patients at high risk of infection (e.g., history of hereditary or acquired immune deficiency disorder, including history of known human immunodeficiency virus [HIV] infection) or with a history of an infected joint prosthesis at any time with that prosthesis still in situ, leg ulcers, indwelling urinary catheter, or persistent or recurrent chest infections
- History of cancer within the last 10 years, except for basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured
- Evidence of clinically uncontrolled respiratory disease. The investigator should review the data from patients' respiratory assessments, including chest x-ray and pulmonary function tests (PFTs), including diffusing capacity for carbon monoxide (DLCO) tests performed during the screening period or within 12 weeks before day 0 if results of prior assessments are available. Available PFT and DLCO assessments must have had values greater than or equal to 60% of predicted for measurements performed and no uncontrolled lung disease. A patient's medical regimen should not have been significantly intensified to control lung disease within 12 weeks before day 0.
- History of chronic respiratory tract infections
- Congestive heart failure, New York Heart Association classification III or IV
- At screening blood tests, any of the following:
    - Aspartate transaminase (AST) >2 × upper limit of normal (ULN)
    - Alanine transaminase (ALT) >2 × ULN
    - Hemoglobin <75 g/L
    - Neutrophils $<1.5 \times 10^9$/L
    - Creatinine clearance (CrCl) <30 mL/min

Definition of New-Onset and Relapsing/Refractory Giant-Cell Arteritis

- New-onset: The new-onset disease cohort includes patients who have been diagnosed within 6 weeks before day 0 using acute-phase reactants, signs/symptoms, and diagnostic criteria
- Relapsing/refractory: (either/or)
    - The relapsing disease cohort includes patients having prior documented diagnosis of giant-cell arteritis as per diagnostic criteria above more than 6 weeks before day 0 and who have active giant-cell arteritis disease defined by acute-phase reactants and signs/symptoms within 6 weeks before day 0
    - The refractory disease patient has had no remission since the diagnosis of disease, as per clinical expectations. Thus, the patient has documentation of prior diagnosis of giant-cell arteritis, as per diagnostic criteria above, more than 6 weeks before day 0; however, presence of acute-phase reactants and signs/symptoms as per above persists within 6 weeks before day 0.

Study Design
The glucocorticoid taper was started at a dose of oral prednisone between 20 mg and 60 mg daily based on prior glucocorticoid dose, disease status, and investigator discretion. The prednisone dose was subsequently tapered over the 26-week double-blind treatment period according to clinical practice and prior clinical trials.[1] Patients starting on 20 mg or 25 mg daily had their doses held at 20 mg or more for the first 3 weeks. Any patient who could not adhere to the protocol-defined steroid taper because of flare/relapse was permitted escape therapy at the discretion of the investigator. During the 12-week washout safety follow-up period, patients could be observed with no additional therapeutic or could be managed with standard of care, which could include corticosteroids, dose modification of corticosteroids, other immunomodulatory agents (with washout period recommended), and/or approved therapies (e.g. tocilizumab), as per the discretion of the investigator.
Study Design reference: 1. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017;**377**(4):317–328.

Procedures
Randomisation, stratified by disease type (new-onset or relapsing/refractory) at baseline, was completed using interactive response technology (Interactive Web Response System). Allocation to treatment groups was done using a central computerized randomisation procedure with a permuted block design and a block size of 5. Patients, investigators, and study personnel were masked to treatment assignments during the study.

Remission was required at the onset of the treatment period to increase the precision in the capture of time to flare (primary outcome) and to streamline the time-to-event statistical analyses.

In addition, the prednisone tapering schedule was designed such that every patient would reach the critical 8-10 mg/day prednisone dose threshold at a similar time frame regardless of the starting dose, thus aligning the time domain for the time-to-event analysis.

Adjudication of Flare
All documented reports of flare were reviewed by an independent, blinded clinical endpoint adjudication committee. Further details are included in the Methods section of the Supplementary Appendix. A contract research organization prepared all documentation of reports of flare that was then reviewed by an independent, blinded clinical endpoint adjudication committee. Flare was defined as a re-increase in acute phase reactants, i.e., CRP level from normal to 1 mg/dL or greater and/or of ESR from less than 20 mm in the first hour to 30 mm or greater, and at least one of the following signs or symptoms attributed by the investigator to new, worsening, or recurrent giant-cell arteritis:

- Cranial symptoms
    - New or recurrent headache or pain or tenderness of the scalp or the temporal artery
    - Visual signs/symptoms, such as ischemic retinopathy, ischemic optic neuropathy, diplopia, amaurosis fugax, etc
    - New or recurrent claudication of the tongue or the masseter muscle, or worsening temporal artery signs and symptoms
    - Transient ischemic attack or stroke related to giant-cell arteritis in the opinion of the investigator
- Extracranial symptoms
    - Classic polymyalgia rheumatica–like symptoms, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness
    - New or recurrent claudication in the peripheral circulation (i.e., in one of the extremities)
    - New or worsening angiographic abnormalities detected via MRI, CT/CTA, or PET-CT of the aorta or other great vessels or via ultrasonography of the temporal arteries

Supportive findings included other symptoms that, in the opinion of the investigator, were related to worsening giant-cell arteritis, such as sustained daily recurrent fever with a temperature over 38°C for more than 1 week, chronic anemia, or unexplained weight loss. All elements of the diagnostic work-up pertinent to the investigator diagnosis of a flare/relapse (i.e., the primary efficacy end point) were then reviewed by an independent blinded clinical endpoint committee.

Management of Treatment of Patients Who Experience Flare

Patients who experienced a flare or who could not adhere to the protocol-defined steroid taper because of a flare were treated to ensure their best possible care as follows:

- The patient discontinued the assigned study drug (mavrilimumab or placebo) and was offered escape therapy in accordance with local standard of care, as determined by the investigator, which included dose modifications of glucocorticoids, other immunomodulatory agents, and/or approved therapies (e.g., tocilizumab). The dosages of all concomitant medications used to treat the flare were noted.

Escape glucocorticoid therapy was escalated immediately. Because of possible safety and pharmacologic effects resulting from overlapping exposures to immunomodulatory agents on top of co-administered glucocorticoids, investigators were asked to consider a washout period of at least 35 days (based on elimination half-lives) after the last dose of study drug if deemed clinically appropriate.

End Points

Other secondary end points organized by hierarchy were as follows: time to elevated ESR by week 26, time to elevated CRP by week 26, time to development of giant cell arteritis signs/symptoms or new/worsening vasculitis on imaging by week 26, cumulative prednisone dose at week 26 (including dose received after flare), percent of patients who completed the prednisone taper and had normal ESR by week 26, percent of patients who completed the prednisone taper and had a normal CRP by week 26, percent of patients who completed the prednisone taper and had no new giant cell arteritis signs/symptoms or new/worsening vasculitis on imaging by week 26, and cumulative glucocorticoid dose at the end of the safety follow-up period (week 38). Time to flare by week 26 and sustained remission at week 26 were also assessed in the subgroups of patients with new-onset and relapsing/refractory disease at baseline, although the study was not powered for this assessment, given the limited sample size. Finally, the proportion of patients with elevated ESR or CRP and without giant cell arteritis flare was assessed in a post hoc analysis.

RESULTS

Additional secondary end points

Median (95% CI) time to elevated ESR was significantly longer for mavrilimumab recipients (26·1 [16·1, NE] weeks) compared to placebo recipients (12·1 [8·1, 16·6] weeks; P=0·028) (Table 3). Median (95% CI) time to elevated CRP level was significantly longer for mavrilimumab recipients (NE [8.1, NE]) compared to placebo recipients (12·3 [3·3, 24·1] weeks; P=0·038). Finally, median (95% CI) time to giant-cell arteritis signs and symptoms or new or worsening vasculitis by imaging was NE (NE, NE) for mavrilimumab recipients and was 25·1 (15·1, NE) weeks for placebo recipients (P=0·065). As significance was not reached with this end point, p-values for all following endpoints in the hierarchy are nominal. The mean cumulative prednisone dose by week 26 was 2074 mg in mavrilimumab recipients and 2403 mg in placebo recipients (nominal P=0.067); least-squares mean difference (nominal 95% CI) was –326 mg (–676 mg to 23 mg). A higher proportion of mavrilimumab recipients completed glucocorticoid tapering and had a normal ESR (45·2% and 14·3%, respectively; nominal P=0·020) or no disease signs and symptoms (71·4% vs. 32·1%; nominal P=0·0031) compared with placebo recipients. The proportion of patients completing glucocorticoid taper with a normal CRP level was numerically

higher for mavrilimumab recipients versus placebo recipients (23·8% and 14·3%; nominal P=0·55); not all patients had locally performed CRP measurements.

Adherence to Prednisone Taper in Patients with Sustained Remission

Five patients did not adhere strictly to the prednisone taper but were included in the calculation as having sustained remission. Three patients (two receiving placebo and one receiving mavrilimumab) adhered to the taper but were still receiving prednisone 1 mg daily instead of 0 mg daily at week 26. A fourth patient receiving mavrilimumab adhered to the taper until non-specific temporal headache prompted the investigator to increase the prednisone dose from 1 mg to 5 mg at week 24; ESR and CRP (central) were not elevated at the time of non-specific headache or during the remainder of the 26-week period and the patient did not meet the protocol definition of flare. Finally, a fifth patient receiving placebo adhered to the taper until scalp paresthesia and increased CRP and ESR led the investigator to increase the prednisone dose from 3 mg to 10 mg at week 17; scalp paresthesia was determined as eczema, and the patient assumed the prednisone taper after that point. All other patients with sustained remission adhered to the prednisone taper.

Adjudication Concordance

One placebo-treated patient developed chronic anemia, unexplained weight loss, and elevated ESR at week 24, which was assessed by the investigator as flare but was not confirmed by adjudication because of the absence of definitive symptoms or positive imaging. Active giant-cell arteritis was diagnosed by imaging (PET-CT) in this patient during the safety follow-up at week 30.

Table S1. Patient-Level Relapse Characteristics.

Patient	Treatment	Time of Relapse (week)	ESR at Time of Flare (mm/h)	CRP at Time of Flare (mg/dL)	Prednisone Dose (mg)	GCA Signs and Symptoms at Time of Flare
1	Mavrilimumab	26.1	73	1.8	60	Imaging consistent with worsening vasculitis
2	Mavrilimumab	16.1	33	6.3	4	Cranial: scalp or temporal artery tenderness; extracranial: symptoms of PMR
3	Mavrilimumab	5.7	15	1.5	30	Cranial: N/O localized headache, unexplained m/j pain upon mastication
4	Mavrilimumab	16.1	45	3.2	20	Extracranial: symptoms of PMR
5	Mavrilimumab	15.4	102	7.6	5	Cranial: N/O localized headache, scalp or temporal artery tenderness, unexplained m/j pain upon mastication; extracranial: symptoms of PMR
6	Mavrilimumab	24.3	30	0.1	0	Cranial: N/O localized headache, unexplained m/j pain upon mastication; extracranial: claudication of the extremities, symptoms of PMR; imaging: consistent with worsening vasculitis
7	Mavrilimumab	5	34	1.4	50	Cranial: unexplained m/j pain upon mastication; extracranial: symptoms of PMR
8	Mavrilimumab	16.4	27	1.4	3	Extracranial: symptoms of PMR; imaging: consistent with worsening vasculitis; supportive: unexplained weight loss
9	Placebo	6.4	12	1.5	20	Cranial: unexplained m/j pain upon mastication; extracranial: symptoms of PMR
10	Placebo	17.1	39	2.4	34	Cranial: N/O localized headache, scalp or temporal artery tenderness; extracranial: symptoms of PMR; imaging: consistent with

						worsening vasculitis, evidence of new large vessel vasculitis
11	Placebo	16.3	25	3.4	5	Cranial: N/O localized headache, scalp or temporal artery tenderness; extracranial: symptoms of PMR; imaging: consistent with worsening vasculitis, evidence of new large vessel vasculitis
12	Placebo	16	101	9.0	5	Cranial: N/O localized headache; extracranial: symptoms of PMR;
13	Placebo	20.1	14	1.2	2	Cranial: N/O localized headache, scalp or temporal artery tenderness; extracranial: symptoms of PMR; imaging: consistent with worsening vasculitis; supportive: unexplained weight loss
14	Placebo	12.3	50	2	5	Extracranial: symptoms of PMR;
15	Placebo	25.1	31	1.1	0	Extracranial: symptoms of PMR; imaging: consistent with worsening vasculitis
16	Placebo	11.4	87	2.8	6	Extracranial: symptoms of PMR; imaging: consistent with worsening vasculitis, evidence of new large vessel vasculitis; supportive: unexplained weight loss
17	Placebo	11.7	11	1.6	7	Extracranial: claudication of the extremities; imaging: consistent with worsening vasculitis, evidence of new large vessel vasculitis
18	Placebo	15.1	31	0.8	10	Cranial: N/O localized headache
19	Placebo	10.9	33	1.0	7	Extracranial: symptoms of PMR
20	Placebo	12.3	51	0.6	15	Extracranial: symptoms of PMR
21	Placebo	17	49	1.1	80	Cranial: N/O localized headache, scalp or temporal artery tenderness, unexplained m/j

	pain upon mastication; extracranial: symptoms of PMR

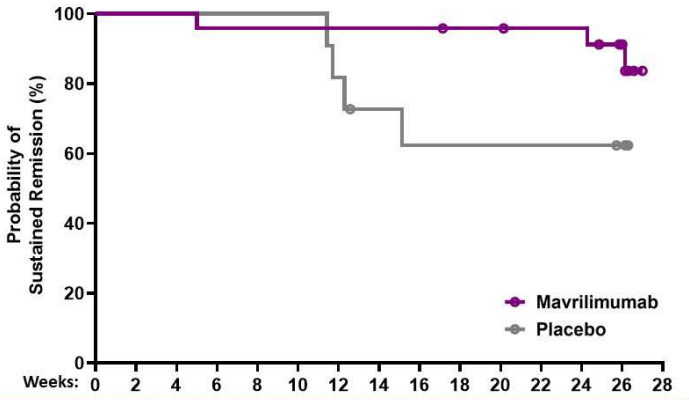
Table S2. Proportions of Patients with Elevations in Acute-Phase Reactants at Time of Flare and without Flare.

Assessment*	Mavrilimumab + 26-wk Prednisone Taper (N=42)	Placebo + 26-wk Prednisone Taper (N=28)	Mavrilimumab + 26-wk Prednisone Taper (N=42)	Placebo + 26-wk Prednisone Taper (N=28)
	Patients with Flare after Remission		Patients without Flare after Remission	
No. of patients (%)	**8 (19·1)**	**13 (46·4)**	**34 (81·0)**	**15 (53·6)**
Presence of elevated C-reactive protein level† or elevated erythrocyte sedimentation rate‡	8 (100·0)	13 (100·0)	20 (58·8)	14 (93·3)
Presence of elevated C-reactive protein level†	7 (87·5)	10 (76·9)	10 (29·4)	11 (73·3)
C-reactive protein level,† mg/dL, median (interquartile range)	1·8 (1·4-6·3)	1·8 (1·2-2·8)	2·6 (1·8-3·0)	2·0 (1·5-3·4)
Presence of elevated erythrocyte sedimentation rate‡	6 (75·0)	9 (69·2)	16 (47·1)	10 (66·7)
Erythrocyte sedimentation rate,‡ mm/hr, median (interquartile range)	40 (33-73)	49 (33-51)	42 (34-62)	54 (42-59)

*Values are no. (%) of patients, except where indicated otherwise.
†Elevated C-reactive protein level (local/central), ≥1 mg/dL.
‡Elevated erythrocyte sedimentation rate, ≥30 mm/hr.

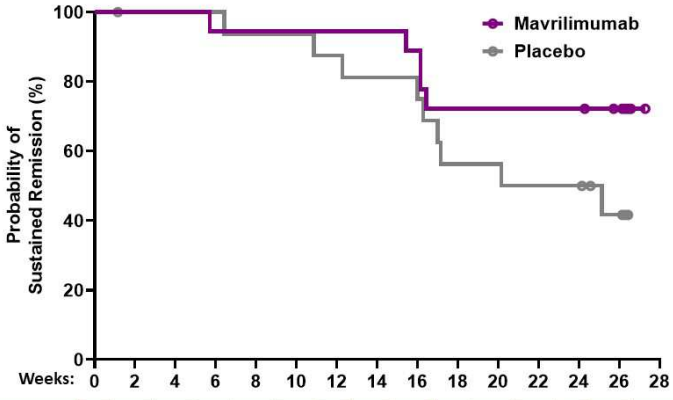
Figure S1. Time to First Flare of Giant-Cell Arteritis in Patients with New-Onset Disease and Patients with Relapsing/Refractory Disease. At baseline, patients had to be in remission (defined as the absence of giant-cell arteritis signs and symptoms and erythrocyte sedimentation rate <20 mm/hr or C-reactive protein level <1 mg/dL) and receiving an oral prednisone dose between 20 mg and 60 mg daily. Patients who discontinued treatment for reasons other than flare were censored for the calculation of time to flare. A) Time to flare in new-onset patients, defined as a diagnosis of giant-cell arteritis within 6 weeks before baseline. The hazard ratio for the comparison of mavrilimumab and placebo was 0.29 with a 95% confidence interval of 0.06 to 1.31. B) Time to flare in relapsing/refractory patients, defined as a diagnosis of giant-cell arteritis more than 6 weeks before baseline. The hazard ratio for the comparison of mavrilimumab and placebo was 0.43 with a 95% confidence interval of 0.14 to 1.30.

A



Mavrilimumab Patients at Risk, n	24	24	24	23	23	23	23	23	23	22	22	21	21	18	0
Placebo Patients at Risk, n	11	11	11	11	11	11	9	7	6	6	6	6	6	5	0

B



Mavrilimumab Patients at Risk, n	18	18	18	17	17	17	17	17	16	13	13	13	13	10	0
Placebo Patients at Risk, n	17	16	16	16	15	15	14	13	13	9	9	8	8	5	0

Figure S2. Sustained Remission Rate of Giant-Cell Arteritis at Week 26 in Patients with New-Onset Disease and Patients with Relapsing/Refractory Disease.

(A) Among the subgroup of patients with new-onset giant cell arteritis at baseline, 91.3% of mavrilimumab recipients and 62.3% of placebo recipients had sustained remission at week 26. **(B)** Among the subgroup of patients with relapsing/refractory disease at baseline, sustained remission at week 26 was observed in 72.2% of mavrilimumab recipients and 41.7% of placebo recipients. The key prespecified secondary efficacy end point of sustained remission was defined as the absence of flare from randomization through week 26. Sustained remission rate was derived by Kaplan-Meier curve analysis.