Mavrilimumab, a Fully Human Granulocyte–Macrophage Colony-Stimulating Factor Receptor α Monoclonal Antibody

Long-Term Safety and Efficacy in Patients With Rheumatoid Arthritis

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Objective. Mavrilimumab, a human monoclonal antibody, targets granulocyte–macrophage colony-stimulating factor receptor α. We undertook to determine the long-term safety and efficacy of mavrilimumab in rheumatoid arthritis patients in 2 phase IIb studies (1071 and 1107) and in 1 open-label extension study (ClinicalTrials.gov identifier: NCT01712399).

Methods. In study 1071, patients with an inadequate response to disease-modifying antirheumatic drugs (DMARDs) received mavrilimumab (30, 100, or 150 mg) or placebo every other week plus methotrexate. In study 1107, patients with an inadequate response to anti–tumor necrosis factor agents and/or DMARDs received 100 mg mavrilimumab every other week or 50 mg golimumab every 4 weeks plus methotrexate. Patients entering the open-label extension study received 100 mg mavrilimumab every other week plus methotrexate. Long-term safety and efficacy of mavrilimumab were assessed.

Results. A total of 442 patients received mavrilimumab (14 of 245 patients from study 1071, 9 of 70 patients from study 1107, and 52 of 397 patients from the open-label extension study discontinued mavrilimumab treatment throughout the studies). The cumulative safety exposure was 899 patient-years; the median duration of mavrilimumab treatment was 2.5 years (range 0.1–3.3 years). The most common treatment-emergent adverse events (AEs) were nasopharyngitis (n = 69; 7.68 per 100 patient-years) and bronchitis (n = 51; 5.68 per 100 patient-years). At weeks 74 and 104, 3.5% and 6.2% of patients, respectively, demonstrated reduction in forced expiratory volume in 1 second, while 2.9% and 3.4% of patients, respectively, demonstrated reduction in forced vital capacity (>20% reduction from baseline to <80% predicted). Most pulmonary changes were transient and only infrequently associated with AEs. Mavrilimumab at 100 mg every other week demonstrated sustained efficacy;

at week 122, 65.0% of patients achieved a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) of <3.2, and 40.6% of patients achieved a DAS28-CRP of <2.6.

Conclusion. **Long-term treatment with mavrilimumab maintained response and was well-tolerated with no increased incidence of treatment-emergent AEs. Safety data were comparable with those from both phase IIb qualifying studies.**

Rheumatoid arthritis (RA) is associated with a high prevalence of comorbidities (1), including increased risk of serious infections (2) and malignancies (1). This is because of the immune system dysregulation intrinsic to the disease and prolonged use of conventional immunosuppressive therapies and targeted biologic agents (2–4).

Granulocyte–macrophage colony-stimulating factor (GM-CSF) is a proinflammatory cytokine involved in RA pathogenesis (5,6). GM-CSF binds to GM-CSF receptor α (GM-CSFRα), thereby reducing macrophage and neutrophil numbers and function in rheumatoid inflammatory lesions (7,8). GM-CSF has a well-established role in hematopoiesis in vitro and in vivo, supporting neutrophilic granulocyte proliferation and differentiation (9,10); however, there is little deficiency in resting hematopoiesis in gene-targeted mice lacking GM-CSF or its receptor (11). This suggests that GM-CSF is not required in vivo for resting hematopoiesis. Patients with RA may still have anemia (12) and occasionally neutropenia (13). In these cases, or in the presence of infection, it is possible that GM-CSF is necessary for adequate granulocyte production, and GM-CSF inhibition may induce neutropenia (14).

GM-CSF is involved in lung homeostasis and promotes alveolar macrophage proliferation (15,16), which has a critical role in lung defense and surfactant homeostasis (17) through catabolism of surfactant lipids and proteins (18). Pulmonary alveolar proteinosis is a rare disease characterized by alveolar surfactant accumulation (19). Polyclonal anti–GM-CSF autoantibodies and mutations in surfactant proteins or GM-CSFR are considered responsible for most cases of pulmonary alveolar proteinosis.

Mavrilimumab is a human monoclonal antibody that blocks GM-CSFRα, acting as a competitive antagonist of GM-CSF signaling (20). It has previously demonstrated efficacy and an acceptable safety profile in RA patients in a 12-week phase IIa study (21) and in 24-week phase IIb studies (22,23) at dosages up to 150 mg every other week.

To evaluate the sustained safety and efficacy of mavrilimumab (including the longitudinal assessment of pulmonary function), we report the long-term (up to >3 years) safety profile in RA patients who participated in 2 phase IIb studies: study 1071 (22) and study 1107 (23). Irrespective of initial treatment allocation, patients were subsequently enrolled in an open-label extension study (study 1109 [ClinicalTrials.gov identifier: NCT01712399]) and received mavrilimumab at 100 mg every other week.

PATIENTS AND METHODS

Study design. This report includes data from a phase II open-label extension study (study 1109 [ClinicalTrials.gov identifier: NCT01712399]) and 2 qualifying phase IIb studies. Studies 1071 (EARTH EXPLORER 1 [ClinicalTrials.gov identifier: NCT01706926]) (22) and 1107 (EARTH EXPLORER 2 [ClinicalTrials.gov identifier: NCT01712399]) (23) were randomized, double-blind, multicenter studies. In study 1071, 326 patients with moderate-to-severe RA who had inadequate responses to disease-modifying antirheumatic drugs (termed DMARD inadequate responders) received subcutaneous (SC) mavrilimumab (30, 100, or 150 mg) or placebo every other week plus standard therapy (methotrexate at 7.5–25.0 mg/week and folic acid at ≥5 mg/week). In study 1107, 138 patients who had a previous inadequate response to DMARDs and/or DMARD inadequate responders for whom 1 or 2 anti–tumor necrosis factor (anti-TNF) agents (excluding golimumab) had failed received SC mavrilimumab at 100 mg every other week or golimumab at 50 mg every 4 weeks plus standard therapy (Figure 1). In study 1107, placebo was administered every other week to patients receiving golimumab to maintain masking.

Patients who completed studies 1071 or 1107 or who had inadequate clinical responses after week 12 were eligible to enter the open-label extension study. All patients enrolled in the open-label extension study received SC mavrilimumab at 100 mg every other week plus standard therapy (Figure 1). Patients received mavrilimumab at 100 mg as this was the highest, most efficacious dose in a previous phase IIa study (21). At initiation of the open-label extension study, no data from study 1071 were available demonstrating improved efficacy and an acceptable safety profile with mavrilimumab at 150 mg versus 100 mg.

All 3 studies were conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice, and all were approved by the appropriate institutional review board or independent ethics committee at each study site. All patients provided written informed consent.

Inclusion and exclusion criteria for patients. Patients were ages 18–80 years with moderate-to-severe adult-onset RA according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria (24), a Disease Activity Score in 28 joints (25) using the C-reactive protein level (DAS28-CRP) of ≥3.2 at screening, a DAS28 using the erythrocyte sedimentation rate of ≥3.2 (26) on day 1, and ≥4 swollen joints at screening and on day 1. Detailed inclusion and exclusion criteria for studies 1071 and 1107 are included in Supplementary Methods, available on the *Arthritis & Rheumatology* web site at http://online library.wiley.com/doi/10.1002/art.40420/abstract.

Patients who completed the treatment period of the qualifying study (1071 or 1107), or who did not have an adequate response to the blinded investigational product at a predefined time point in the qualifying study despite their initial randomization, were eligible to enroll in the open-label extension study.
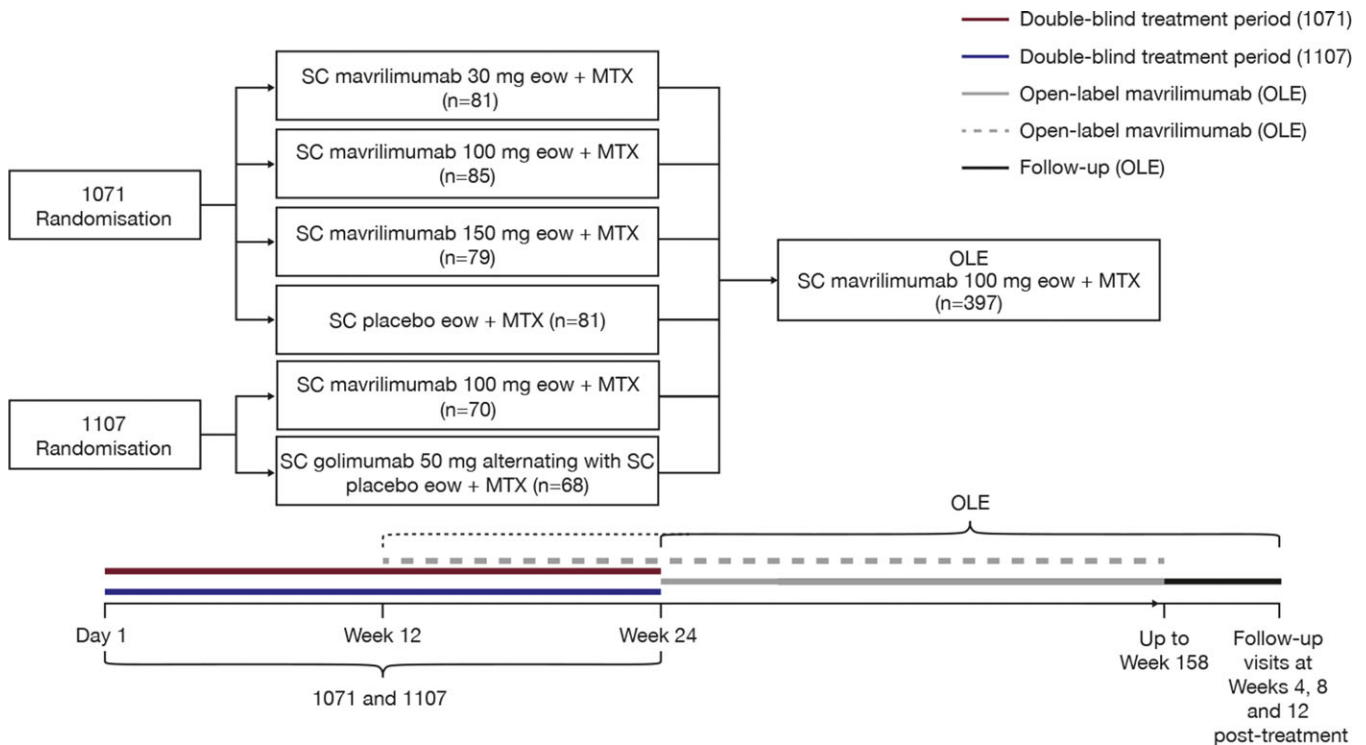
Figure 1. Designs of the phase IIb studies (1071 and 1107) and the open-label extension study (OLE). After week 24, patients enrolled in study 1071 or study 1107 were eligible for the open-label extension study and received mavrilimumab for up to a maximum of 3.3 years. After week 12, patients enrolled in study 1071 or study 1107 who were not responding adequately to blinded study treatment were allowed to enter the open-label extension study to receive mavrilimumab. Studies 1071 and 1107 were not conducted simultaneously. SC = subcutaneous; eow = every other week; MTX = methotrexate.

However, ≤12 weeks had to elapse since their completion/withdrawal visit in the qualifying study. Other key inclusion criteria for the open-label extension study were receipt of a stable dose of conventional DMARDs (chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, or leflunomide) ≥4 weeks prior to the first mavrilimumab dose, if patients were receiving treatment with these drugs, and no evidence of clinically uncontrolled respiratory disease (confirmed by a pulmonologist who reviewed patient data from respiratory assessments, including a chest radiograph and pulmonary function tests performed at screening; the patient must have had forced expiratory volume in 1 second/forced vital capacity [FEV$_1$/FVC] ≥60% of predicted values). Key exclusion criteria for the open-label extension study included permanent discontinuation of investigational product in either qualifying study, receipt of B cell–depleting therapies during or after discontinuation from the qualifying studies, and discontinuation of non–cell depleting biologic DMARDs within 8 weeks of day 1 of the open-label extension study. Stable dosages of oral corticosteroids, analgesics, and nonsteroidal antiinflammatory drugs were permitted.

Analysis sets. The overall phase as-treated population included all mavrilimumab-treated patients in studies 1071 or 1107 or in the open-label extension study. The open-label as-treated population included all 100 mg mavrilimumab–treated patients in the open-label extension study.

Safety analysis. Long-term safety of mavrilimumab was assessed by evaluating treatment-emergent adverse events (AEs), treatment-emergent serious AEs (SAEs), treatment-emergent AEs of special interest (events of scientific and medical interest specific to understanding of the investigational product and requiring rapid communication with the sponsor [hepatic function abnormality, acute and delayed hypersensitivity reactions, clinically relevant pulmonary abnormality, neutropenia {absolute neutrophil count <1.0 × 10^9/liter}, malignancy, and infection]), and laboratory measurements in the overall as-treated population. The severity of all events was determined by the investigator.

Lung function abnormalities and pulmonary AEs were assessed in the overall as-treated population. Pulmonary monitoring was conducted throughout all studies, including serial standardized lung function testing (FEV$_1$/FVC), assessments of dyspnea (using the Borg Dyspnea Index [27]), and chest radiographs. While assessment of diffusing capacity for carbon monoxide (DL$_{CO}$) was performed in most patients included in the open-label extension study, this test was not available at the start of the 2 qualifying randomized studies due to initial standardization difficulties. Therefore, baseline DL$_{CO}$ % predicted data were only collected in 48 patients from study 1107 and in no patients from study 1071, which limited full interpretation of the results. A blinded Independent Pulmonary Evaluation Committee (IPEC) adjudicated any patient with a pulmonary abnormality (pulmonary AE/SAE and/or abnormalities on pulmonary function tests and DL$_{CO}$ considered clinically relevant) for the presence of pulmonary alveolar proteinosis.

Efficacy analysis. The long-term clinical efficacy of mavrilimumab was evaluated as an exploratory objective. Efficacy

end points included proportions of patients achieving a DAS28-CRP of <3.2 and <2.6 (overall as-treated population), proportions of patients meeting the ACR 20% improvement criteria (achieving an ACR20 response) (28) or achieving an ACR50 or ACR70 response at weeks 74, 98, and 122 (as-treated population in the open-label extension study), Clinical Disease Activity Index (CDAI) (29) remission rates at weeks 74, 98, and 122 (as-treated population in the open-label extension study), radiographic progression assessed by change from baseline in the modified Sharp/van der Heijde score (SHS) (30) through week 74 (as-treated population, only including patients from study 1071), and patient-reported outcomes (overall as-treated population), including the Health Assessment Questionnaire disability index (31), Short Form 36 health survey (32), and Functional Assessment of Chronic Illness Therapy–Fatigue subscale (33).

Biomarker analysis. For a complete understanding of mavrilimumab's molecular mechanism of action, biomarkers related to the GM-CSF pathway were analyzed in all patients participating in study 1107 who enrolled in the open-label extension study. GM-CSF is believed to drive production of thymus and activation–regulated chemokine (TARC)/CCL17 (34) and macrophage-derived chemokine (MDC)/CCL22 (35), and serum concentrations of CCL17 and CCL22 were suppressed by mavrilimumab but not by golimumab in the qualifying 1107 study (36). Serum CCL17/TARC and CCL22/MDC concentrations were measured by enzyme-linked immunosorbent assay on days 1, 8, 29, 85, 169, 225, 253, 337, and 393 and are reported herein.

Statistical analysis. Safety and patient-reported outcome data were summarized descriptively. Exposure-corrected incidence rates for AEs and AEs of special interest were used, expressed as number of patients experiencing an event per 100 patient-years.

Proportions of patients achieving a DAS28-CRP of <3.2 and <2.6 and ACR20/ACR50/ACR70 response rates were calculated using the number of patients with an assessment at each visit as the denominator and the number of responders as the numerator. The CDAI was defined as the sum of the tender joint count (using 28 joints), the swollen joint count (using 28 joints), the patient's global assessment of disease activity (on a 0–10-cm visual analog scale [VAS]), and the physician's global assessment of disease activity (on a 0–10-cm VAS). CDAI remission was defined as a score of ≤2.8. Change in SHS is presented using a cumulative incidence plot at week 74.

RESULTS

Patients. Randomization for study 1071 began September 11, 2012; the last patient was evaluated January 29, 2014. In study 1107, patients were randomized from March 19, 2013; the last patient was evaluated February 6, 2015. The first patient entered the open-label extension study February 11, 2013; the last patient visit was completed December 30, 2015.

Across the 3 studies, 442 patients received mavrilimumab (overall as-treated population). Of these, 409 (92.5%) consented to participate in the open-label extension study; 12 were ineligible (primarily due to inclusion/exclusion criteria) and did not receive treatment. Therefore, the open-label as-treated population included 397

Table 1. Baseline demographic and disease characteristics of the patients (as-treated population)*

Open-label extension study (n = 397)†	
Demographic characteristics‡	
Age, mean ± SD years	51.1 ± 11.2
Female, no. (%)	339 (85.4)
Race, no. (%)	
White	364 (91.7)
American Indian/Alaska Native	29 (7.3)
Other§	4 (1.0)
Disease characteristics‡	
RA duration, mean ± SD years	7.9 ± 6.8
Prior biologic DMARD therapy, no. (%)¶	100 (25.1)
Stopped because of loss of efficacy	47 (11.8)
Stopped because of safety/other#	53 (13.4)
MTX dosage, mean ± SD mg/week	14.8 ± 3.8
Corticosteroid dosage, mean ± SD mg/week**	5.4 ± 1.5
DAS28-CRP, mean ± SD	4.3 ± 1.6
HAQ DI score, mean ± SD	1.2 ± 0.6
Swollen joint count, mean ± SD	7.2 ± 7.9
Tender joint count, mean ± SD	14.0 ± 13.8
CRP, geometric mean mg/liter (CV %)	4.7 (170)
ESR, geometric mean mm/hour (CV %)	27.9 (62)
Studies 1071 and 1107 (n = 442)	
Disease characteristics	
DAS28-CRP, mean ± SD	5.8 ± 0.8
HAQ DI score, mean ± SD	1.6 ± 0.5
Swollen joint count, mean ± SD	15.7 ± 8.4
Tender joint count, mean ± SD	26.3 ± 12.6
CRP, geometric mean mg/liter (CV %)	6.0 (181)
ESR, geometric mean mm/hour (CV %)	36.8 (52)
Pulmonary disease characteristics	
Concomitant pulmonary diseases, no. (%)††	
Asthma	17 (3.8)
COPD	8 (1.8)
Other	21 (4.8)
Ever smoked, no. (%)	134 (30.3)
Current smokers, no. (%)	76 (17.2)
RF and ACPA positive, no. (%)	359 (81.2)
FEV_1, mean ± SD % predicted	93.9 ± 14.7
FVC, mean ± SD % predicted	94.0 ± 14.6
DL_{CO}, mean ± SD % predicted (n)‡‡	72.4 ± 9.3 (48)
Borg Dyspnea Index score, mean ± SEM	0.4 ± 0.0

* RA = rheumatoid arthritis; MTX = methotrexate; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; HAQ DI = Health Assessment Questionnaire disability index; CV = coefficient of variation; ESR = erythrocyte sedimentation rate; COPD = chronic obstructive pulmonary disease; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
† An 8-week washout period occurred prior to the open-label extension study. Patients who did not have a response to mavrilimumab were also included in the open-label extension study.
‡ Baseline values were obtained from predosing in studies 1071 and 1107.
§ Black, Asian, African American, Native Hawaiian, or other Pacific Islander.
¶ Patients were counted only once for each disease-modifying antirheumatic drug (DMARD).
# Other reasons include discontinuation because of lack of initial efficacy, expense of medication, or because the medication was given only in a clinical trial.
** Derived from 234 of 397 patients (59%) who received concomitant corticosteroids.
†† Clinically relevant uncontrolled pulmonary disease was an exclusion criterion for all 3 studies.
‡‡ Diffusing capacity for carbon monoxide (DL_{CO}) data were not collected during study 1071 and were not collected in all patients in study 1107; baseline values were available for 48 of 397 patients in the open-label extension study.

patients, of whom 345 (86.9%) were being treated at study closure. Throughout the studies, 14 of 245 patients from study 1071, 9 of 70 patients from study 1107, and 52 of 397 patients from the open-label extension study discontinued mavrilimumab treatment (see Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract). A drug survival curve is shown in Supplementary Figure 2, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract. Baseline demographic and disease characteristics of the patients are summarized in Table 1.

Safety analysis findings. Across the 3 studies, patients had a cumulative mavrilimumab safety exposure of 899 patient-years and a median treatment duration of 2.5 years (range 0.1–3.3 years). The majority of AEs were mild or moderate, with 44 patients (10.0%) in the overall as-treated population reporting a treatment-emergent AE of grade ≥3 severity. The most frequently reported treatment-emergent AEs and treatment-emergent SAEs in the overall phase are shown in Table 2. There were no reports of monocytopenia. Neutropenia was reported in 4 patients (2 with grade 1, 1 with grade 2, 1 with grade 3; 0.45 per 100 patient-years), and 14 patients reported serious infections (1.56 per 100 patient-years). One event of neutropenia (not recorded as an AE of special interest) was considered serious and was associated with an SAE of urinary tract infection that resolved with standard therapy. Pulmonary events of special interest occurred in 83 patients (a full breakdown is shown in Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract). The most frequent was bronchitis; 2 cases of active pulmonary tuberculosis infection were reported (0.22 per 100 patient-years), and 1 was bacteriologically confirmed. Neither patient had active or latent tuberculosis at screening or had previously received anti-TNF agents for RA treatment. There were no cases of pulmonary alveolar proteinosis or findings suggestive of pulmonary alveolar proteinosis (confirmed by the IPEC).

Treatment-emergent AEs leading to discontinuation were reported in 12 patients (3.0%) in the open-label as-treated population (see Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract). Three deaths were reported during the open-label extension study, 1 due to a car accident and 2 due to cardiopulmonary failure. One of the 2 patients with cardiopulmonary failure was hospitalized for a few days before death (apparently to treat sepsis subsequent to a biliary tract infection); the other patient died suddenly. None of these deaths was considered related to mavrilimumab treatment. There were no clinically relevant shifts in laboratory values for the overall phase.

Pulmonary function and long-term pulmonary safety analysis findings. The mean Borg Dyspnea Index score in the overall as-treated population remained

Table 2. Summary of treatment-emergent AEs, treatment-emergent SAEs, and treatment-emergent AEs of special interest (as-treated population for the overall phase) in patients receiving 100 mg mavrilimumab every other week (n = 442), with a cumulative mavrilimumab safety exposure of 899 patient-years*

Summary of treatment-emergent AEs†	
Patients reporting ≥1 treatment-emergent AE, no. (%)	335 (75.8)
Treatment-emergent AEs in ≥15 patients, no. (rate per 100 patient-years)	
Nasopharyngitis	69 (7.68)
Bronchitis	51 (5.68)
Hypertension	38 (4.23)
Rheumatoid arthritis	44 (4.90)
Upper respiratory tract infection	38 (4.23)
Headache	31 (3.45)
Urinary tract infection	40 (4.45)
Influenza	29 (3.23)
Pharyngitis	20 (2.23)
Osteoarthritis	17 (1.89)
Diarrhea	21 (2.34)
Back pain	15 (1.67)
Gastroenteritis	15 (1.67)
Summary of treatment-emergent SAEs†	
Patients reporting ≥1 treatment-emergent SAE, no. (%)	60 (13.6)
Treatment-emergent SAEs in ≥2 patients, no. (rate per 100 patient-years)	
Osteoarthritis	4 (0.45)
Bronchitis	4 (0.45)
Rheumatoid arthritis	4 (0.45)
Anemia	3 (0.33)
Pulmonary tuberculosis	2 (0.22)
Gastroenteritis	2 (0.22)
Pneumonia	2 (0.22)
Urinary tract infection	2 (0.22)
Cardiopulmonary failure	2 (0.22)
Myocardial infarction	2 (0.22)
Cholelithiasis	2 (0.22)
Uterine leiomyoma	2 (0.22)
Deaths, no. (%)	3 (0.7)
Summary of treatment-emergent AEs of special interest†	
Patients reporting ≥1 treatment-emergent AE of special interest, no. (%)	114 (25.8)
Treatment-emergent AEs of special interest, no. (rate per 100 patient-years)	
Hepatic function abnormalities	2 (0.22)
Hypersensitivity reactions	13 (1.45)
Serious infections	14 (1.56)
Malignancies	5 (0.56)
Neutropenia	4 (0.45)
Pulmonary events‡	83 (9.24)

* Includes all patients exposed to mavrilimumab in studies 1071 and 1107 or in the open-label extension study. AEs = adverse events; SAEs = serious AEs.
† Includes AEs with onset after the first mavrilimumab dosage.
‡ All were reviewed by an Independent Pulmonary Evaluation Committee.

unchanged at week 134 compared with week 74 (Table 3). Similar dyspnea scores from baseline through week 134 were observed in the populations of patients who switched to 100 mg mavrilimumab from 30 mg mavrilimumab, 150 mg mavrilimumab, 50 mg golimumab, or placebo.

Table 3. Borg Dyspnea Index score and reductions from baseline in pulmonary function test results (as-treated population for the overall phase) in patients receiving 100 mg mavrilimumab every other week (n = 442)*

Borg Dyspnea Index score (measure of breathlessness), mean ± SEM (n)	
Week 12†	NA
Week 74	0.3 ± 0.0 (279)
Week 134	0.3 ± 0.0 (58)
Pulmonary function test results‡	
>20% reduction from baseline to <80% predicted FEV$_1$, no./total no. (%)	
Week 12†	2/298 (0.7)
Week 74	8/231 (3.5)
Week 104	11/178 (6.2)
Week 130	1/29 (3.4)
>20% reduction from baseline to <80% predicted FVC, no./total no. (%)	
Week 12†	2/298 (0.7)
Week 74	7/239 (2.9)
Week 104	6/177 (3.4)
Week 130	0/32 (0.0)

* Includes all patients who received mavrilimumab in studies 1071 and 1107 or in the open-label extension study. NA = not available; FEV$_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity.
† Between weeks 12 and 24, 3 patients receiving 150 mg mavrilimumab (3.8%), 8 patients receiving 100 mg mavrilimumab (9.4%), 12 patients receiving 30 mg mavrilimumab (14.8%), and 37 patients receiving placebo (45.7%) transferred from study 1071 to the open-label extension study because of lack of efficacy. Between weeks 12 and 24, 2 patients receiving 100 mg mavrilimumab (2.9%) and no patients receiving 50 mg golimumab (0.0%) transferred from study 1107 to the open-label extension study because of lack of efficacy.
‡ Reported events do not necessarily overlap between time points.

A small proportion of patients experienced an event defined as clinically relevant (>20% decrease from baseline and <80% predicted) reduction in lung function (FEV$_1$ and FVC). At weeks 74 and 104, 3.5% and 6.2% of patients, respectively, demonstrated reduction in FEV$_1$, while 2.9% and 3.4% of patients, respectively, demonstrated reduction in FVC (>20% reduction from baseline to <80% predicted) (Table 3). In most cases, these events occurred at a single time point and were not associated with a respiratory AE. Mean FEV$_1$, FVC, and DL$_{CO}$ values remained within 5% of the mean baseline value for patients treated during the randomized phases of the phase IIb studies (Figure 2); however, baseline DL$_{CO}$ values were measured in a minority of patients (48 patients and 0 patients in studies 1107 and 1071, respectively).

Efficacy analysis findings. In exploratory analyses, patients demonstrated sustained efficacy with mavrilimumab treatment. At week 122, a total of 117 patients (65.0%) achieved low disease activity with a DAS28-CRP of <3.2, and 73 patients (40.6%) achieved a DAS28-CRP of <2.6 (overall as-treated population). DAS28-CRP <3.2 and <2.6 response rates are shown in Figures 3A and B. Patients treated with 100 mg mavrilimumab also demonstrated sustained ACR20/ACR50/ACR70 responses (Figure 3C).

There was an increase in the number of patients with CDAI remission over time in the open-label extension study (see Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract). After 74 weeks, 54% of patients demonstrated no radiographic progression (≤0.5-point change in SHS compared with baseline values) (see Supplementary Figure 3, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract). The mean change in SHS from baseline to week 74 was 1.40. Improvements from baseline in patient-reported outcome end points were also observed and maintained with mavrilimumab treatment (see Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract).

Biomarker analysis findings. In study 1107, serum TARC/CCL17 and MDC/CCL22 concentrations were suppressed in patients treated with 100 mg mavrilimumab, but not in patients treated with 50 mg golimumab (see Supplementary Figure 4, http://onlinelibrary.wiley.com/doi/10.1002/art.40420/abstract). These results were observed in patients with an inadequate response to DMARDs (≥1 failed regimen) and in those with an inadequate response to anti-TNF (1–2 failed regimens, excluding golimumab). After an 8-week washout period prior to the open-label extension study, TARC/CCL17 and MDC/CCL22 concentrations returned to baseline. However, in the open-label extension study, mavrilimumab treatment suppressed TARC/CCL17 and MDC/CCL22 concentrations regardless of treatment received in study 1107.

DISCUSSION

We evaluated the safety of long-term mavrilimumab treatment in patients with RA and demonstrated that it is well tolerated, with most treatment-emergent AEs mild or moderate in severity. Low incidences of neutropenia (0.90%; 0.45 per 100 patient-years) and serious infections (3.17%; 1.56 per 100 patient-years) were observed in the overall as-treated population; there were no reports of monocytopenia. Both reported deaths due to cardiopulmonary failure were considered unrelated to mavrilimumab treatment. Previous studies of mavrilimumab evaluated treatment for ≤24 weeks; herein, we have shown that long-term mavrilimumab treatment generated safety data comparable with those from the phase IIb qualifying studies (22,23).

RA affects pulmonary function, and lung disease is a major contributor to patient morbidity and mortality (37,38). Disease may affect all lung areas, and the majority of patients demonstrate low total lung capacity and FVC (39). Pulmonary comorbidities may arise because of chronic immune activation, increased susceptibility to infections (often related to immunomodulatory medications), or direct toxicity from DMARDs or biologic therapies (40);
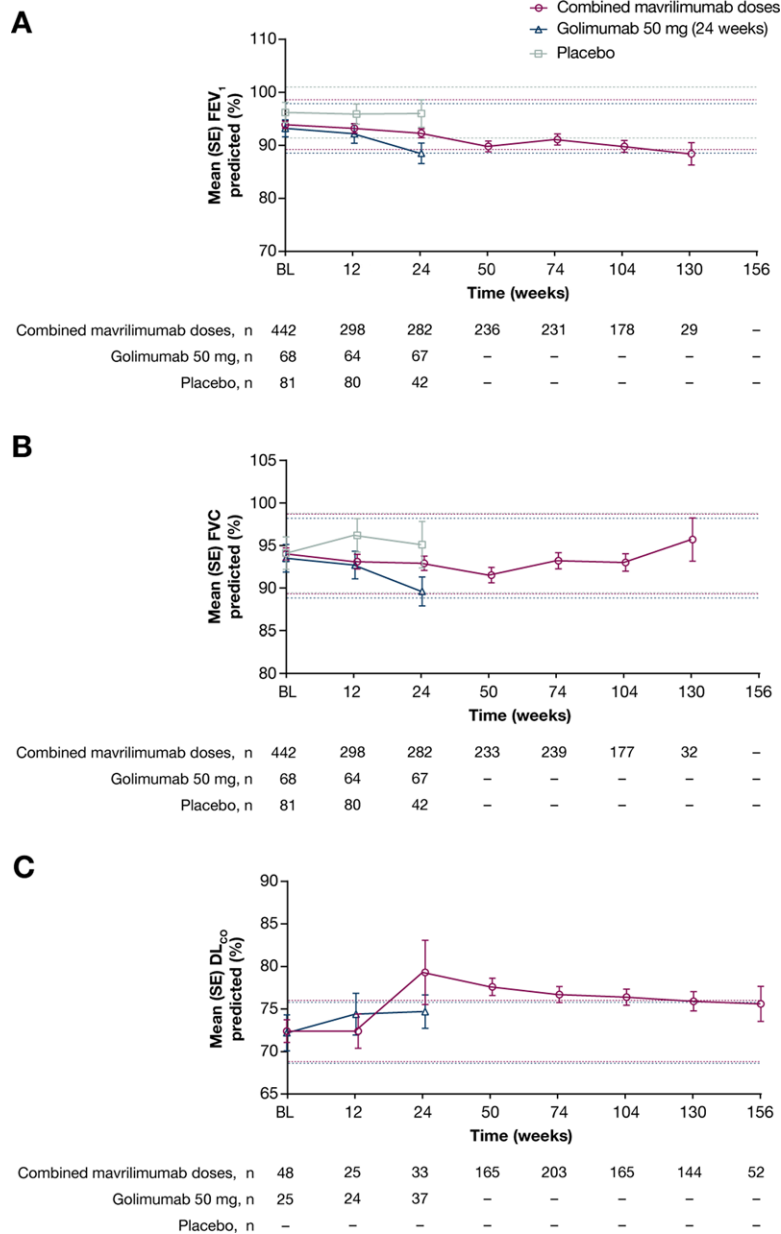
Figure 2. Pulmonary function values over time (as-treated population for the overall phase). **A,** Forced expiratory volume in 1 second (FEV$_1$). **B,** Forced vital capacity (FVC). **C,** Diffusing capacity for carbon monoxide (DL$_{CO}$). Dotted lines represent 5% above and below baseline values for FEV$_1$, FVC, and DLco. Between weeks 12 and 24, 3 patients receiving 150 mg mavrilimumab (3.8%), 8 patients receiving 100 mg mavrilimumab (9.4%), 12 patients receiving 30 mg mavrilimumab (14.8%), and 37 patients receiving placebo (45.7%) transferred from study 1071 to the open-label extension study (study 1109) because of lack of efficacy (<20% improvement in both the swollen and tender joint counts compared with day 1). Between weeks 12 and 24, 2 patients receiving 100 mg mavrilimumab (2.9%) and no patients receiving 50 mg golimumab (0.0%) transferred from study 1107 to study 1109 because of lack of efficacy. Following the decision of the sponsor to discontinue study 1109, patients' exposure to a study drug/placebo ranged from 2 to 156 weeks, depending on their date of entry and reason for withdrawal from the studies. For final time points in which n ≤ 5, results were not shown because the number of patients was too low to enable meaningful interpretation. DLco data were not collected during study 1071, and during study 1107 baseline (BL) values were collected in only 48 patients.

however, there are few long-term data concerning changes in pulmonary function with progressive RA. Minor alterations in pulmonary function have been observed in

patients receiving long-term low-dose methotrexate (41); however, another study demonstrated that mean changes in FEV$_1$, FVC, and DLco after 2 years of treatment with
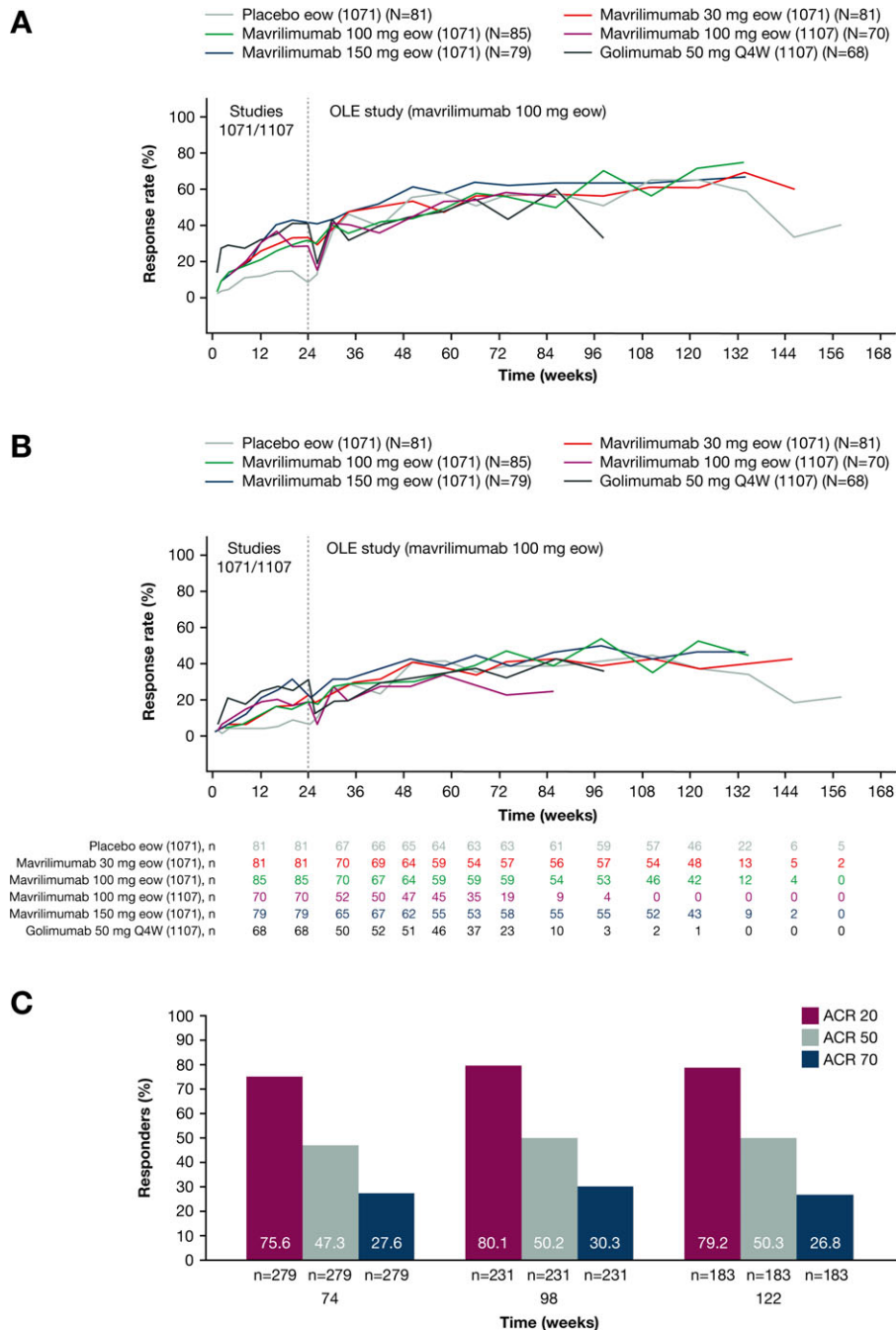
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Legend:
- Placebo eow (1071) (N=81)
- Mavrilimumab 100 mg eow (1071) (N=85)
- Mavrilimumab 150 mg eow (1071) (N=79)
- Mavrilimumab 30 mg eow (1071) (N=81)
- Mavrilimumab 100 mg eow (1107) (N=70)
- Golimumab 50 mg Q4W (1107) (N=68)

Studies 1071/1107 | OLE study (mavrilimumab 100 mg eow)

B

Legend:
- Placebo eow (1071) (N=81)
- Mavrilimumab 100 mg eow (1071) (N=85)
- Mavrilimumab 150 mg eow (1071) (N=79)
- Mavrilimumab 30 mg eow (1071) (N=81)
- Mavrilimumab 100 mg eow (1107) (N=70)
- Golimumab 50 mg Q4W (1107) (N=68)

Studies 1071/1107 | OLE study (mavrilimumab 100 mg eow)

Placebo eow (1071), n	81	81	67	66	65	64	63	63	61	59	57	46	22	6	5
Mavrilimumab 30 mg eow (1071), n	81	81	70	69	64	59	54	57	56	57	54	48	13	5	2
Mavrilimumab 100 mg eow (1071), n	85	85	70	67	64	59	59	59	54	53	46	42	12	4	0
Mavrilimumab 100 mg eow (1107), n	70	70	52	50	47	45	35	19	9	4	0	0	0	0	0
Mavrilimumab 150 mg eow (1071), n	79	79	65	67	62	55	53	58	55	55	52	43	9	2	0
Golimumab 50 mg Q4W (1107), n	68	68	50	52	51	46	37	23	10	3	2	1	0	0	0

C

Legend:
- ACR 20
- ACR 50
- ACR 70

Week 74: 75.6 (n=279), 47.3 (n=279), 27.6 (n=279)
Week 98: 80.1 (n=231), 50.2 (n=231), 30.3 (n=231)
Week 122: 79.2 (n=183), 50.3 (n=183), 26.8 (n=183)

Figure 3. **A** and **B,** Proportions of patients with a Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) of <3.2 (**A**) and proportions of patients with a DAS28-CRP of <2.6 (**B**) (data split by original randomized treatment; as-treated population for the overall phase). **C,** Proportions of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) or achieving an ACR50 or ACR70 response at weeks 74, 98, and 122 (as-treated population for the open-label extension [OLE] study). All visits with at least 5 patients are shown. From week 24, initial treatment was switched to 100 mg mavrilimumab every other week (eow). Q4W = every 4 weeks.

low-dose oral methotrexate were comparable with those observed with placebo (42).

We showed that mean FEV_1, FVC, and DLco values remained within 5% of mean baseline values for the overall phase; therefore, pulmonary deterioration was not evident with long-term mavrilimumab treatment in addition to standard therapy. Full DLco data that included baseline values were only available for a limited

proportion of patients. While patients with uncontrolled pulmonary disease were excluded from all studies analyzed, those with less severe disease, such as asthma and chronic obstructive pulmonary disease, were permitted. Hence, although these studies may not completely represent the RA patient population, these data are representative of the majority of patients with RA.

Mavrilimumab competitively antagonizes GM-CSF signaling through GM-CSFRα blockade. Abrogation of GM-CSF signaling in alveolar macrophages may cause surfactant metabolism abnormalities (43), accumulation of which could cause pulmonary alveolar proteinosis, a rare disease with potentially life-threatening consequences (44). Our adjudicated individual data demonstrate that long-term treatment with 100 mg mavrilimumab every other week with concomitant methotrexate was not associated with pulmonary alveolar proteinosis. In the qualifying studies, no clinically relevant differences in pulmonary function were observed between different mavrilimumab dosages and placebo up to week 24 in study 1071, and between mavrilimumab and golimumab up to week 24 in study 1107. Long-term controlled comparisons of the treatment regimens cannot be made beyond this time point since all patients included in the open-label extension study were treated with 100 mg mavrilimumab every other week; however, it should be noted that a clinically relevant and generally transient reduction in FEV_1 or FVC was only experienced by a small number of patients beyond week 24. Furthermore, discontinuation due to pulmonary events in the open-label phase was low.

We observed clinically meaningful long-term efficacy in patients receiving mavrilimumab for up to >3 years across many disease activity parameters. Biomarker analyses demonstrated sustained suppression of 2 GM-CSF pathway–related protein markers following mavrilimumab treatment, regardless of previous treatment received. These results support data from previous studies (22,23), confirming that TARC/CCL17 and MDC/CCL22 specifically relate to the GM-CSF pathway and indicating a potential benefit of inhibiting this pathway in RA treatment.

This analysis had a number of limitations. The extension phase was not randomized or controlled; therefore, we were unable to evaluate the long-term safety and efficacy of mavrilimumab in comparison with a reference population of patients with RA. Furthermore, the population was reduced because of discontinuations from the 2 qualifying studies and ineligibility of patients who did not meet inclusion criteria. However, the analysis conformed to the EULAR recommendations for reporting rheumatology clinical trial extension studies (45). The open-label

extension study dosage of 100 mg mavrilimumab every other week was selected to be consistent with the highest and most efficacious dosage in a previous phase IIa study (21). However, data analysis from study 1071 (conducted while the open-label extension study was ongoing) demonstrated that 150 mg mavrilimumab was more effective in DMARD inadequate responders (22), which suggests that a suboptimal dosage was used in the open-label extension study. Consequently, the study was discontinued.

To our knowledge, this study is unique, as multiple pulmonary function tests were performed in a systematic, long-term, longitudinal manner. No new safety signals or evidence of clinically meaningful lung function deterioration were seen with long-term mavrilimumab treatment. Long-term mavrilimumab treatment was also associated with clear and sustained benefits in measures of RA disease outcomes. In light of the results from study 1071 (22), we advocate phase III studies with mavrilimumab (at 150 mg every other week) in RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Burmester had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Burmester, McInnes, Kremer, Godwood, Michaels, Guo, Close, Weinblatt.
Acquisition of data. Miranda, Vencovský, Godwood, Albulescu, Guo, Close.
Analysis and interpretation of data. Burmester, McInnes, Kremer, Vencovský, Godwood, Albulescu, Michaels, Guo, Close, Weinblatt.

ADDITIONAL DISCLOSURES

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