Magnetic Resonance Imaging of the Joint and Evaluation of the Granulocyte–Macrophage Colony-Stimulating Factor/CCL17 Axis in a Phase IIa Randomised Mechanistic Study of Otilimab in Patients with Rheumatoid Arthritis

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Summary (646 words)

Background. Otilimab is a human monoclonal antibody that inhibits granulocyte–macrophage colony-stimulating factor (GM-CSF), a driver in many immune-mediated inflammatory conditions. We evaluated the effect of otilimab on the GM-CSF/CCL17 axis and synovitis in patients with rheumatoid arthritis (RA).

Methods. This Phase IIa, randomised, double-blind, multicentre, placebo-controlled, parallel-group study was performed at nine sites across the USA, Poland, and Germany. Patients aged ≥18 years with RA per ACR/EULAR criteria and receiving stable methotrexate were randomised (3:1) by interactive response technology system to either subcutaneous otilimab 180 mg or placebo once weekly for 5 weeks, then every other week (EOW) until week 10 (giving a treatment period of 12 weeks), followed by a 10-week safety follow-up. Randomisation was stratified by early RA (≤2 years since diagnosis) and established RA (>2 years since diagnosis). Patients and study personnel (except for an unblinded coordinator/nurse who prepared and administered the study drug) were blinded to treatment assignment; the syringe was shielded during administration. Patients were enrolled by study investigators and allocated to a treatment via central randomisation based on a schedule generated by the Sponsor. The primary endpoint was change over time (assessed at baseline and weeks 1, 2, 4, 6, 8, 12, and 22 [follow-up]) in >100 biomarkers, including target engagement biomarkers and those that may be indicative of RA disease activity and response to otilimab. Secondary endpoints were change from baseline in synovitis, osteitis and erosion assessed by RA magnetic resonance imaging (MRI) scoring system (RAMRIS) and RA MRI quantitative score (RAMRIQ), and safety evaluation. The primary, secondary and safety endpoints were assessed in the intent-to-treat population. Biomarker and MRI endpoints were analysed for differences between treatment groups using a repeated measures model. This study is complete (ClinicalTrials.gov: NCT02799472).

Findings. Between 9 August 2016 and 30 October 2017, 39 patients were randomised and included in the analysis (otilimab n=28; placebo n=11). In the otilimab group, mean (95% CI) serum levels of GM-CSF/otilimab complex peaked at week 4 (138·4 ng/L; 90·0, 212·9) but decreased from week 6–12. CCL17 levels decreased from baseline to week 1, maintained to week 8 and returned to baseline at week 12; least squares (LS) mean (95% confidence interval [coefficient of variation] ratio to baseline was 0·65 (0·49, 0·86 [13·60]) at week 2, 0·68 (0·53, 0·88 [12·51]) at week 4, 0·78 (0·60, 1·00 [12·48]) at week 6 and 0·68 (0·54, 0·85 [11·21]) at week 8. No meaningful change in CCL17 levels was observed with placebo. In the otilimab arm, the LS mean ratio to baseline in MMP-degraded Type I collagen was 0·86–0·91 over weeks 1–8, returning to baseline at week 12; levels remained above baseline at all time points in the placebo group. There were no observable differences between otilimab and placebo for all other biomarkers. At week 12, LS mean (SE) CFB in RAMRIS synovitis score was −1·3 (0·60) in the otilimab group and 0·8 (1·17) with placebo; RAMRIQ synovitis score showed a LS mean (SE) CFB of −1417·0 µl (671·54) in the otilimab group and −912·3 µl (1405·77) with placebo. Compared with placebo, otilimab showed numerically larger, statistically non-significant reductions from baseline to week 12 in RAMRIS synovitis, osteitis and bone erosion and in RAMRIQ synovitis and erosion damage. Adverse events were reported in 11/28 [39%] otilimab-treated and 4/11 [36%] placebo-treated patients, most commonly cough in the otilimab arm (2/28 [7%]; not reported in placebo arm), and pain in extremity and RA in the placebo arm (4/11 [36%] and 2/11 [18%], respectively; not reported in otilimab arm). There were no serious adverse events or deaths.

Interpretation. Serum levels of GM-CSF/otilimab complex indicated that target engagement was achieved with initial weekly dosing, but not sustained with EOW dosing. CCL17 may be a pharmacodynamic biomarker for otilimab activity in future studies. Otilimab was well tolerated and, despite suboptimal exposure, improved synovitis over 12 weeks in patients with active RA.

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Key words: rheumatoid arthritis, anti-GM-CSF monoclonal antibody, CCL17, synovitis, magnetic resonance imaging

Research in context

Evidence before this study

We performed a PubMed search for clinical trials published between 2000 and 2016, i.e. prior to study start, using the search terms “rheumatoid arthritis” AND “anti-GM-CSF” OR “anti-GMCSF” OR “namilumab” OR “mavrilimumab” OR “MOR103” with no restriction on language. We identified four clinical trials: one proof-of-concept trial of otilimab (MOR103) and 3 Phase I/II/IIa trials for mavrilimumab. Both agents showed efficacy of targeting granulocyte–macrophage colony-stimulating factor (GM-CSF) or its receptor in the treatment of rheumatoid arthritis (RA). Although one mavrilimumab study assessed a panel of 12 biomarkers and showed an increase in inflammatory biomarkers, no extensive biomarkers analysis had been performed in clinical trials of patients with RA treated with anti-GM-CSF. In addition, none of the mavrilimumab studies included assessment of inflammation via magnetic resonance imaging (MRI). As such, there was a need to conduct a mechanistic study to assess the effect of anti-GM-CSF treatment on a wider range of biomarkers, and on inflammation as assessed by MRI. Given the promising findings of the otilimab proof-of-concept study, further assessment of clinical efficacy following otilimab treatment in patients with RA was also warranted.

Added value of this study

This study adds to the evidence of GM-CSF as a viable target in the treatment of RA. Treatment with otilimab decreased CCL17 levels and an early and sustained improvement in pain visual analogue scale score. Preclinical studies suggest that the GM-CSF/CCL17 axis may have a role in mediating pain – this study provides preliminary evidence for this role in patients with RA. In addition, a trend towards improvement in synovial inflammation (assessed by MRI) was observed with otilimab.

Implications of all the available evidence

The findings of the current study support the rationale for the further clinical development of otilimab as a treatment option for patients with RA. Additionally, the effect of otilimab on CCL17 indicates that CCL17 shows promise as a pharmacodynamic biomarker for otilimab in future studies. The effect of otilimab on pain outcomes also warrants further study.

Introduction

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a haemopoietic growth factor that can act as a cytokine that exerts many pro-inflammatory effects on myeloid cells,[1] and is a key driver in a broad range of immune-mediated conditions.[1,2] In a murine collagen-induced arthritis model of rheumatoid arthritis (RA), GM-CSF promoted inflammation, whilst GM-CSF-deficient mice were protected against arthritis,[3] and there was a dose-dependent reduction in arthritis scores after anti-GM-CSF receptor antibody treatment.[4]

In pathological conditions, GM-CSF is produced by multiple cell types in response to immune activation.[1] GM-CSF levels are elevated in the synovial fluid of some patients with RA,[5,6] and several studies have demonstrated that GM-CSF exacerbates myeloid cell activation to produce cytokines, including interleukin (IL)-6, IL-1, and tumour necrosis factor, and induces and perpetuates inflammation, which can cause severe tissue damage.[1,7] In addition, increased macrophage numbers in the RA synovial tissue have been correlated with disease activity and radiographic evidence of disease progression;[8-10] their numbers and activation state are partly controlled by GM-CSF.[6]

Targeting GM-CSF is therefore a promising therapeutic strategy in RA. Otilimab (also known as GSK3196165, MOR103 and MOR04357) is a high-affinity recombinant human monoclonal immunoglobulin G1 antibody that specifically binds to and inhibits human GM-CSF.[1,11] The binding of GM-CSF to either otilimab or the GM-CSF receptor-alpha (GM-CSFRα) subunit is mutually exclusive;[11] therefore, otilimab blocks GM-CSF from binding to the GM-CSFRα subunit, thus inhibiting GM-CSF activity.[11] Recent Phase Ib/IIa/IIb clinical trials in patients with RA have indicated that inhibition of GM-CSF signalling results in clinical benefit.[12-14]

The GM-CSF → JMJD3 (a histone demethylase) → IRF4 (interferon regulatory factor 4) → CCL17 (chemokine [c-c motif] ligand 17) pathway is active in monocytes/macrophages, and mouse models have indicated that CCL17 is required for GM-CSF-mediated pain and arthritic disease.[7,15] CCL17 levels were elevated in synovial fluid from some patients with RA compared with those with osteoarthritis.[16] We explored the effect of anti-GM-CSF antibody treatment on the GM-CSF/CCL17 axis and synovial inflammation, shown by magnetic resonance imaging (MRI), in a mechanistic clinical trial in patients with RA. MRI is an effective method to assess synovial inflammation,[17] and has been used in clinical trials of effective[18] and ineffective[19] treatments for RA.

Methods

Study design

This Phase IIa, randomised, multicentre, double-blind, placebo-controlled study was conducted at nine sites across the USA, Poland, and Germany and in compliance with the International Conference on Harmonisation Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from relevant ethics committees or institutional review boards (Ethikkomission der Aerztekammer des Saarlandes; Komisja Bioetyczna przy Okregowa Izba Lekarska; Schulman Associates Institutional Review Board, Inc.). See **Supplementary Methods** for protocol amendments approved prior to study start, and protocol deviations during the study. The full study protocol can be found at: https://clinicaltrials.gov/ct2/show/NCT02799472.

Patients

Eligible patients (≥18 years of age) met classification criteria for RA per American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria,[20] and had active disease (despite previous disease-modifying anti-rheumatic drug [DMARD] treatment) defined by ≥4 each of swollen and tender joints and disease activity score for 28 joints with C-reactive protein (DAS28(CRP)) ≥3·2 at screening, signs of inflammation on an MRI scan (assessed locally), and CRP ≥3·0 mg/L. Patients had to be taking a stable dose of methotrexate (MTX) ≥4 weeks prior to Day 1. Patients were excluded if they had a history of other immunoinflammatory disorders or any respiratory disease, including significant interstitial lung disease (such as pulmonary fibrosis, chronic obstructive pulmonary disease, moderate-severe asthma, bronchiectasis, previous pulmonary alveolar proteinosis [PAP]), or a clinically significant persistent cough or unexplained unstable dyspnoea that could compromise patient safety. See **Supplementary Methods** for full inclusion and exclusion criteria. Patient recruitment was carried out by study investigators. All patients provided written informed consent.

Randomisation and masking

Patients were randomised (3:1) to otilimab 180 mg or placebo. Patients were allocated to treatment via central randomisation based on a randomisation schedule generated by the Sponsor using validated randomisation

software. Patients were enrolled by study investigators and assigned randomisation numbers via an interactive response technology system. Randomisation was stratified by early RA (≤2 years since diagnosis) and established RA (>2 years since diagnosis).

Study investigators, study staff (other than an unblinded treatment administrator), patients and sponsor were blinded to treatment allocation. The radiologist was blinded to patient name, exam date (including chronology of exams), randomisation arm, and investigator site identifiers. To ensure adequate blinding of treatment allocation, an unblinded study coordinator or nurse prepared and administered the study medication. During administration, the syringe barrel was shielded to ensure all other study site personnel, the patient and the sponsor were blinded to treatment. In the event of an emergency, serious medical condition or related unexpected serious adverse event (SAE), treatment assignment could be unblinded by the investigator or treating physician. GlaxoSmithKline (GSK) Global Clinical Safety and Pharmacovigilance staff could also unblind treatment codes. If the treatment allocation code was unblinded, the patient was withdrawn from the study. Although not formally assessed, there were no reports of unblinding during the study.

Procedures

Otilimab 180 mg or placebo was administered by subcutaneous injection once a week for 5 weeks, then every other week (EOW) until week 10, followed by a 12-week follow-up period (**Supplementary Figure 1**). All patients received MTX 7·5–25 mg/week at a stable dose and folic/folinic acid ≥5 mg/week during the treatment period. See **Supplementary Methods** for treatment withdrawal/interruption guidelines. To assess change from baseline (CFB) in prespecified biomarkers (centrally assessed), blood samples were collected at screening, before dosing at baseline, and at weeks 1, 2, 4, 6, 8, 12, and 22 (all assessed biomarkers are provided in **Supplementary Table 1**). Serum concentrations of CCL17 (MesoScale Diagnostics, Rockville, MD) and C1M (Nordic Bioscience, Herlev, Denmark) were measured using validated immunoassay methods.

For pharmacokinetic (PK) assessment, blood samples were collected before dosing at baseline and weeks 1, 2, 4, 6, 8, 12, and 22, and analysed for serum concentration of otilimab using an electrochemiluminescence immunoassay.

The impact of otilimab on synovitis was assessed using MRI by the RA MRI score (RAMRIS, blinded expert single reader),[21] RA MRI quantitative assessment (RAMRIQ)[18] and dynamic contrast-enhanced MRI (DCE-MRI) in the most affected hand/wrist (based on local-site MRI assessment), measured at screening and weeks 4, 12, and 22. RAMRIS synovitis was scored on a scale of 0−3 across 8 joints (maximum score 24). DCE-MRI data analysis was performed using heuristic analysis (maximal enhancement [*ME*] and initial rate of enhancement [*IRE*])[22] and PK modelling using the extended Tofts model to extract the exchange rate [K^{trans}] of the contrast agent from blood plasma to the extracellular extravascular space.[23] The effects of otilimab on bone erosion and osteitis were assessed by RAMRIS and RAMRIQ, and on cartilage loss and joint-space narrowing by cartilage loss score (CARLOS)[24] and RAMRIQ, respectively. See **Supplementary Methods** for all scanning procedures and analyses.

Clinical efficacy assessments included DAS28(CRP), swollen joint count in 66 joints, tender joint count in 68 joints, Clinical Disease Activity Index, ACR20 and EULAR response,[20] and patient-assessed pain visual analogue scale (VAS). Improvements in physical function was assessed using the Health Assessment Questionnaire-Disability Index. Clinical efficacy assessments were measured at screening, baseline, and weeks 1, 2, 3, 4, 6, 8, 10, 12, and 22.

Safety parameters were monitored throughout the study, including AEs and SAEs, infections, and anti-drug antibodies. AEs lasting ≥15 days of cough (Grade ≥2), dyspnoea (Borg Scale Grade ≥3) and decrease from baseline >15% in diffusing capacity or transfer factor of the lung for carbon monoxide (D_{LCO}) were adjudicated by an independent external pulmonary expert. Pulmonary events lasting ≥15 days with no clear explanation were reviewed by the pulmonary adjudication panel to assess possible cases of PAP. Blood samples for immunogenicity were collected at baseline, weeks 2, 4, and 12, week 22 follow-up, and at the early withdrawal visit for patients who discontinued study medication prematurely; samples were assessed for presence of anti-otilimab antibodies.

Outcomes

The primary endpoint was the CFB in prespecified biomarkers. Secondary endpoints assessed safety (incidence of AEs, SAEs, AEs of special interest, and immunogenicity) and inflammatory structural joint damage (CFB in synovitis, osteitis and erosion via RAMRIS and RAMRIQ in the most affected hand/wrist).

Several exploratory endpoints were also assessed. Clinical efficacy endpoints included CFB in ACR20/50/70, DAS28(CRP) score and remission rates. PK/target engagement endpoints included serum levels of otilimab, free GM-CSF, and GM-CSF:otilimab complex. Additional MRI endpoints were CFB in joint inflammation assessed by the DCE-MRI parameters K^{trans}, interstitial volume, plasma volume, *IRE* and *ME,* and CFB in cartilage loss and joint-space narrowing via CARLOS and RAMRIQ, respectively.

Statistical analysis

Sample size calculations were not pre-specified for the primary endpoint as there were no defined targets on which to assess sample size; the number of patients enrolled was considered appropriate to assess changes in key biomarkers. For RAMRIS synovitis data the standard deviation (SD) for both groups was assumed to have a value of 2·5.[25-27] Based on this value, with 30 patients on otilimab 180 mg and 10 patients on placebo, aiming for 50% early (<2 years) and 50% established patients with RA, it was estimated that the lower and upper bounds of the 95% confidence interval (CI) for the difference would be within 1·8 points of the difference. This was considered the worst-case precision and further estimates assuming different weights for the prior distribution on placebo were assessed to estimate any improvement in the precision of the CI.

The primary and safety population was the intent-to-treat population, defined as all patients randomised to treatment and who received ≥1 dose of study drug. The PK population was defined as all patients randomised to treatment who received ≥1 dose of otilimab 180 mg and have ≥1 quantifiable otilimab concentration data available. Biomarkers, MRI, and continuous efficacy endpoints were analysed for treatment differences using a repeated measures model; the model was fit with fixed effects for treatment group, disease duration (≤2 years or >2 years), visit, treatment by visit interaction and baseline, and visit within subject as a repeated effect. In addition, RAMRIS synovitis was analysed with a repeated measures Bayesian model for the difference between treatment groups at each visit using a non-informative prior to estimate the posterior median (95% credible interval). Binary clinical efficacy endpoints were planned to be assessed using a logistic regression model including terms for treatment group, disease duration (≤2 years or >2 years) and baseline value; however, due to low numbers of responders in the placebo arm no analyses were performed and binary endpoints were summarised descriptively. For each of the clinical efficacy evaluations of binary endpoints, patients with missing efficacy data or early withdrawals (as well as those who received >10 mg/day of oral corticosteroids, new use of parenteral corticosteroids or an intra-articular corticosteroid injection) were imputed as non-responders and therefore treated as a failure.

Statistical significance was defined as 5% two-sided. Statistical analyses were performed using SAS v.9·4 software. No interim analyses were planned. This study (RENAISSANCE; GSK study number: 205180) is registered with ClinicalTrials.gov: NCT02799472. An independent data monitoring committee monitored the study.

Role of the funding source

This study was sponsored by GSK, which was involved in study design and conduct together with authors and investigators. Clinical data were collected by investigators and their teams and GSK. All authors, including those employed by the funder, were involved in data analysis, interpretation of results and the preparation, review and approval of this manuscript. All authors had full access to all the data, contributed to writing/reviewing of the report, and approved the final submitted version. The corresponding author had full access to all the data and the final responsibility to submit for publication.

RESULTS

The study was initiated on 9 August, 2016 and completed on 30 October, 2017. Eighty-eight patients were screened and 39 patients met the entry criteria and were randomised: placebo n=11, otilimab n=28. Seven (64%) patients in the placebo group and 23 (82%) in the otilimab group completed the study (**Figure 1**). Overall, 7/11 (64%) patients in the placebo group and 25/28 (89%) in the otilimab group received at least seven of the eight planned doses; no patient missed more than one dose during the trial. Mean (SD) drug exposure was 63·8 (28·9) days in the placebo group and 79·2 (12·7) days in the otilimab group. The mean weekly dose of MTX was 15·7 mg (SD 4·76) for the placebo group and 17·5 (SD 4·36) for the otilimab 180 mg group; no patients changed MTX dose during the study.

Baseline demographic and clinical characteristics are shown in **Table 1**. Most patients were female 34/39 (87%) and white 33/39 (85%). Mean body mass index was higher in the placebo group (31·5 kg/m^2) than the otilimab group (30·4 kg/m^2); other characteristics were generally balanced. Only 8/39 (21%) patients had RA disease duration ≤2 years; therefore, no analyses of early versus established RA were conducted. After randomisation, baseline synovitis assessment using the RAMRIS scoring system was performed by a single, central, independent reader; a similar proportion of patients in both treatment groups had low level synovitis at baseline, with 3/11 (27%) in the placebo group and 6/28 (21%) in the otilimab group scoring <5/24 in RAMRIS assessment of synovitis.

In the otilimab group, the CCL17 least squares (LS) mean (95% CI [coefficient of variation]) ratio to baseline decreased at week 1; at week 2 it was 0·65 (0·49, 0·86 [13·60]), representing a 35% reduction. This reduction was maintained at week 4 (0·68; 0·53, 0·88 [12·51]), week 6 (0·78; 0·60, 1·00 [12·48]), and week 8 (0·68; 0·54, 0·85 [11·21]). At week 12, CCL17 LS mean increased towards baseline (**Figure 2A**). Further increases were observed after 12 weeks of follow-up. In the placebo group, mean CCL17 levels were at or above baseline values at all time points, except week 2. No correlation between CCL17 levels and ACR50 response or observed pain score was observed (data not shown). Levels of C1M (MMP-degraded Type I collagen) were reduced in the otilimab group (LS mean ratio to baseline: 0·86–0·91 over weeks 1–8); however, levels were restored to baseline at week 12. C1M LS mean levels remained above baseline throughout the study in patients in the placebo group. There were no observable differences between otilimab and placebo in the geometric mean or LS mean observations for all other assessed biomarkers (**Supplementary Table 2**).

RAMRIS synovitis score showed a LS mean (standard error; SE) CFB to week 12 of −1·3 (0·60) in the otilimab group and 0·8 (1·17) in the placebo group; the difference from placebo was −2·2 (95% CI −4·9, −0·5 [p=0·112]) (**Table 2**). At week 12, a reduction in RAMRIS synovitis score was seen in 9/24 (38%) patients in the otilimab group and no patients in the placebo group (**Figure 3A**). One patient in the placebo arm had major worsening to week 12 in RAMRIS synovitis compared with other placebo patients. As a sensitivity analysis, when this patient was excluded from analyses, the difference between otilimab and placebo in RAMRIS synovitis at week 12 with this patient was −2·5 (−5·4, 0·4), and without this patient was −0·7 (−3·5, 2·2). However, Bayesian analyses that included an informative prior on the placebo response showed a posterior median of the difference between otilimab and placebo of −1·95 (−4·41, 0·53).

A greater reduction from baseline to week 12 in the PK DCE-MRI parameter K^{trans} was observed in the otilimab group versus placebo (−0·0140, 95% CI −0·0266, −0·0013 [p=0·031]) (**Figure 3A; Table 2**), and analysis of heuristic DCE-MRI parameters *IRE* and *ME* showed a greater CFB to week 12 with otilimab versus placebo (−0·0006 μMs^{-1}, 95% CI −0·0012, 0·0000 [p=0·051] for *IRE* and −0·0648 mM, 95% CI −0·1297, 0·0001 [p=0·050] for *ME*; **Table 2**). Representative MRI images of a patient receiving otilimab are shown in **Figure 3B**. No statistically significant effects were seen in structural parameters for RAMRIS or RAMRIQ (**Table 2**). Compared with placebo, otilimab showed numerically larger but non-significant reductions from baseline to week 12 in RAMRIS osteitis and bone erosion, and in RAMRIQ synovitis and erosion damage. LS mean (SE) differences from placebo were: −0·8 (−3·2, 1·6 [p=0·521]) for RAMRIS osteitis; −0·4 (−1·5, 0·7 [p=0·475]) for RAMRIS bone erosion; −504·8 μL (−3730·4, 2720·9 [p=0·749]) for RAMRIQ synovitis; and −0·0004 (−0·0028, 0·0021 [p=0·771]) for RAMRIQ erosion damage. All imaging endpoints for all time points are shown in **Supplementary Table 3**.

The overall AE rate was balanced between groups (4/11 [36%] placebo vs 11/28 [39%] otilimab) (**Table 3**), and all were mild or moderate. Two moderate AEs were reported in ≥10% of patients, both in the placebo arm: pain in extremity (placebo 2/11 [18%], otilimab 0/28 [0%]) and rheumatoid arthritis (placebo 2/11 [18%], otilimab 0/28 [0%]). One AE of special interest (neutropaenia Grade ≥3) was reported in the otilimab group, which was considered unrelated to the study treatment. The event lasted for 14 days and was resolved; this patient did not experience any other AEs. There were no SAEs, deaths, AEs leading to dose reduction or drug discontinuation, serious infections, malignancies, major adverse cardiac events, venous thromboembolism, or immunogenicity, no positive anti-drug antibodies, and no clinically meaningful changes in haematology parameters (including neutrophils or serum chemistry).

No clinically meaningful observations for dyspnoea or cough were observed. One patient in the otilimab group experienced D_{LCO} decrease from 72% (predicted value) at baseline to 52% (predicted value) at 12-week follow-up, representing a clinically significant change, and meeting the criteria for reporting of a persistent (≥15 consecutive days) decrease from baseline in D_{LCO} of >15%. However, there were no clinical symptoms associated with this observation; the patient was asymptomatic without complaints of cough or dyspnoea. Lung high-resolution computed tomography showed "fine reticulations within the upper lung fields and also mild bronchiectasis"; per radiologist's opinion, these may have represented manifestations of RA. The independent

pulmonary adjudication panel excluded the possibility of PAP and noted diffuse upper lobe ground glass opacification not associated with traction bronchiectasis or volume loss, indicating the event was not a fibrotic process. Given no previous X-ray abnormalities, the adjudication panel concluded the findings represented an acute infiltrate, with possible aetiologies being acute lung injury/diffuse alveolar damage or atypical infection. There were no pleural effusions to support a diagnosis of pulmonary oedema.

Target engagement of otilimab with GM-CSF was assessed via levels of soluble GM-CSF/otilimab complex and free soluble GM-CSF. In the otilimab group, the geometric mean concentration of GM-CSF/otilimab complex increased during weekly dosing, to a maximum of 138·4 ng/L (95% CI 90·0, 212·9) at week 4; concentrations declined during fortnightly dosing (weeks 6–12), suggesting a reduction in target engagement (**Figure 2B**). GM-CSF/otilimab complex levels remained below the lower limit of quantification (LLoQ) in the placebo group at all scheduled visits. Levels of free GM-CSF were below the LLoQ (0·781 ng/L) at baseline for all patients and remained below the LLoQ for 96% of all assessments; low levels of free GM-CSF (<19 ng/L) were detected in the serum of 2 patients at screening and 3 patients in the otilimab group during the treatment period.

PK analysis was based on samples from 21 patients in the PK population. The serum concentration of otilimab at baseline was below LLoQ (40 ng/mL) in all samples. During weekly dosing, median (min, max) pre-dose serum concentrations of otilimab increased from 1320 (20, 5010) ng/mL at week 1 to a maximum of 2710 (626, 5710) ng/mL at week 4. Concentrations dropped after transitioning to dosing EOW (weeks 6–10), reaching a median (min, max) concentration of 1050 (251, 3400) ng/mL at week 12 (**Supplementary Table 4**). These pre-dose concentrations are lower than expected based on data from healthy volunteer studies (GSK data on file).

Clinical efficacy endpoints showed improvement with otilimab versus placebo at week 12, although statistical analyses were not possible for binary endpoints and statistical significance was not reached for other endpoints (**Table 2**). A significant improvement in DAS28(CRP) was observed with otilimab versus placebo at weeks 6 and 8 (LS mean change difference from placebo: −1·64; 95% CI −2·81, −0·47 [p=0·0075] and −1·00; 95% CI −1·97, −0·02 [p=0·045], respectively), with separation of effect as early as week 1 (**Figure 3C**). No further improvement in DAS28(CRP) was observed from approximately 6 weeks onwards, although the changes remained clinically meaningful through the subsequent duration of the study.

The otilimab treatment group reported a LS mean (SE) change in patient-assessed pain VAS from baseline at week 12 of −14·7 (5·11) in the otilimab group and 1·3 (9·68) in placebo group (**Table 2**). The effect was observed as early as week 1: otilimab −14·9 (3·67) and placebo 3·2 (6·3) (**Supplementary Figure 2**). ACR response rates were consistently higher in the otilimab group versus placebo. The greatest difference in ACR20 response rate was reported at week 8: an ACR20 response was achieved in 10/28 (36%) otilimab-treated patients and in 0/11 placebo-treated patients (difference vs placebo: 35·7%; 95% CI 18·0, 53·5). The response was similar at week 12, when an ACR20 response was achieved in 9/28 (32%) otilimab-treated patients and in 1/11 (9%) placebo-treated patients (difference vs placebo: 23·1%; 95% CI −1·2, 47·3).

DISCUSSION

This Phase IIa experimental medicine clinical trial investigated the effect of otilimab 180 mg (targeting the GM-CSF ligand) on levels of soluble biomarkers, synovial inflammation by means of MRI, and traditional clinical endpoints in patients with RA receiving concomitant MTX. Treatment with otilimab led to a decrease in CCL17 levels from baseline to week 1, which was maintained to week 8 before increasing towards baseline at week 12; no such decrease was evident in the placebo group. Similarly, a reduction in synovitis score in patients receiving otilimab was greater than in the placebo group. Otilimab was well tolerated, and efficacy measures indicated an early effect on disease activity. Analysis of soluble biomarker data including serum levels of GM-CSF/otilimab complex indicate that target engagement peaked at week 4 but dropped after switching to dosing once EOW, indicating that full target engagement was not achieved with this dosing regimen. This finding was supported by the PK results, with pre-dose otilimab concentration reaching a maximum at week 4 then dropping after switching to the less frequent dosing schedule. The pre-dose concentrations in this study were similar to those observed in a Phase IIb dose-ranging study (BAROQUE, GSK study number 201755; ClinicalTrials.gov Identifier: NCT02504671) of otilimab plus MTX in patients with RA,[13] but are lower than expected based on historic data from healthy volunteers (GSK data on file) – this discrepancy is likely due to the high apparent clearance of otilimab.[28]

CCL17 is thought to contribute to the inflammation and pain associated with arthritis,[7,15] although the precise mechanisms are not fully understood. Experiments on GM-CSF-dependent inflammatory pain and arthritis pain and disease in mouse models have shown there is a GM-CSF → JMJD3 → IRF4 → CCL17 pathway, and that absence/inhibition of these mediators ameliorates pain and disease.[15,29] In this study, a reduction in serum CCL17

was observed as early as week 1 in patients receiving otilimab and was maintained until week 8. These findings are consistent with published data showing suppression of CCL17 in patients with RA following blockade of the GM-CSFRα subunit.[30] Taken together, these findings support the view that CCL17 can be regulated by GM-CSF, and that CCL17 levels can be reduced by neutralising GM-CSF. This work also supports the rationale for future studies on CCL17 as a pharmacodynamic biomarker of otilimab activity. Although there was no evidence of correlation between CCL17 and clinical response in the current study, further exploration in larger clinical trials is warranted. Ongoing trials will evaluate whether neutralising CCL17 itself impacts pain in patients with knee OA and in healthy volunteers via evoked pain tests (NCT03485365 and NCT04114656).

At mean level, the majority of other biomarkers did not show observable changes compared with placebo following treatment with otilimab in this study. This might be related to the lower than anticipated serum concentrations of otilimab or biomarker assay sensitivity in some cases. These biomarkers may warrant further investigations in future studies with higher levels of drug exposure.

All imaging measures of synovitis (RAMRIS, RAMRIQ and DCE-MRI) demonstrated a reduction at week 12 in patients treated with otilimab. RAMRIS synovitis and DCE-MRI parameters K^{trans}, *IRE* and *ME* appear to be the most sensitive to treatment-effect in this study. No statistically significant progression of structural damage (erosion and cartilage loss) was observed with MRI, suggesting a positive treatment effect, but the number of patients per study group was relatively small. The improvement seen in synovitis due to otilimab treatment, although consistent, was small in some cases.

Otilimab demonstrated clinical efficacy, with DAS28(CRP) showing a rapid improvement that peaked at week 4. Although there were no further improvements in DAS28(CRP) from week 6 onwards, after switching from dosing every week to EOW, the improvement remained clinically relevant until the last study visit at week 12. The DAS28(CRP) week 12 results were similar to those observed with otilimab 180 mg in a Phase IIb dose-ranging study (BAROQUE) of otilimab plus MTX in patients with RA.[13]

Otilimab was well tolerated and associated with a satisfactory safety profile in patients with active RA. Notably, no meaningful infections or pulmonary events were observed, and no deaths were reported during the study.

A limitation of this experimental medicine study is the relatively small number of patients per treatment group, which may partly explain why only a small improvement in synovitis was observed. Small sample sizes are typical for a mechanistic Phase IIa study, and therefore only large treatment improvements would be expected to be demonstrable. There was an imbalance in baseline DMARD use between treatment groups, and it is surprising that, of the patients randomised to placebo (9 of whom had established RA), only one patient was receiving DMARD therapy (chloroquine). This may reflect a possible single/small centre number bias in treatment decisions. However, other baseline demographics such as DAS28(CRP) were balanced between groups, so any impact on the results is likely to be minimal. In addition, the low baseline RAMRIS synovitis score in some patients may have decreased the ability to detect a measurable improvement in synovitis. Also, RAMRIS and CARLOS results were based on assessments by a single radiologist rather than average scores from two independent radiologists' readings. The results presented here support the rationale for the ongoing Phase III studies with larger patient populations, of longer duration and with an optimised dosing regimen to allow a more comprehensive assessment of the impact of otilimab treatment in patients with RA (ClinicalTrials.gov Identifiers: NCT03980483, NCT03970837 and NCT04134728).

In conclusion, lower than predicted exposure was observed in this study, resulting in suboptimal exposure during the fortnightly dosing period, which was reflected in a lower concentration of GM-CSF/otilimab complex. Inhibition of GM-CSF also resulted in a decrease in CCL17 levels, which indicates that CCL17 could be a valuable pharmacodynamic biomarker of otilimab activity in future clinical trials. Interestingly, the GM-CSF/CCL17 axis may also play a role in mediating pain. Overall, otilimab demonstrated clinical efficacy including significant reduction in pain with a trend towards a reduction in synovial inflammation and was well tolerated in patients with RA.

Author contributions

MCG, PGC, KD, DI, RJ, ML, NM, JP, JES, RW, and PPT contributed to the conception and/or design of the study. MB contributed to the acquisition of data. MCG, PGC, KD, DI, EF, AG, RJ, ML, AR, CP, JP, DS, JES, RW, and PPT, contributed to data analysis and/or interpretation of the data. All authors were involved in development of the manuscript and approved the final version.

Declaration of interests

MCG has received consulting fees or other remuneration from GSK and is an employee and stockholder of SVP Inflammation Development Gilead Sciences. MB reports no conflicts of interest. PGC has received consulting fees or other remuneration from AbbVie Inc., GSK, Lilly, Novartis, and Pfizer Inc., and has served on Speaker's Bureau for Bristol-Myers Squibb, Novartis, Pfizer, and Roche. AMR was an employee of Bioxydyn Ltd at the time of study initiation. CP is an employee and stockholder of Spire Sciences, Inc., has received consulting fees or other remuneration from AbbVie, Five Prime, Genentech, Modern Bioscience, Myriad, Novartis, Roche, Set Point, and Vorso, and has served on Speaker's Bureau for Amgen and Bristol-Myers Squibb. KD, DI, AG, RJ, ML, JP, DS, and JES are employees and stockholders in GSK. AR, EF, NM, RW, and PPT were employees and stockholders of GSK at the time of study conduct.

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Data sharing statement

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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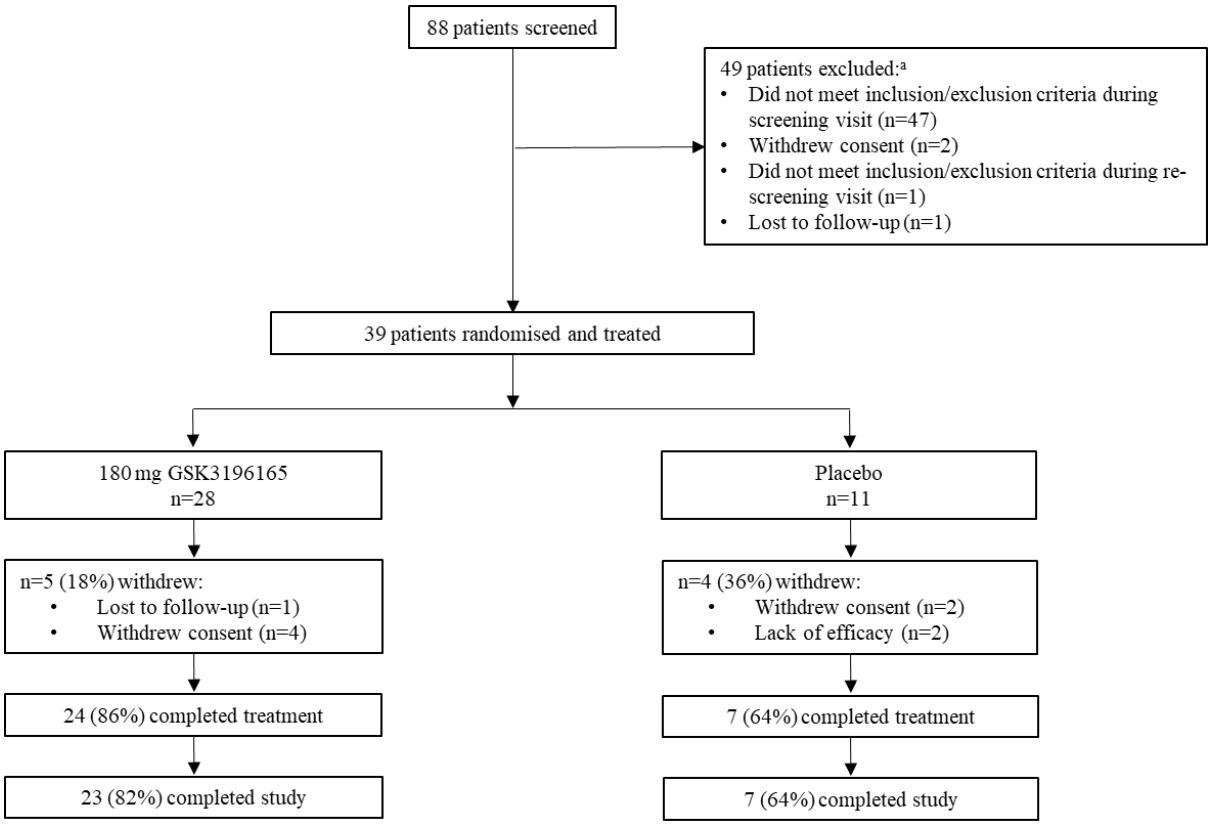
REFERENCES

1. Wicks IP, Roberts AW. Targeting GM-CSF in inflammatory diseases. *Nat Rev Rheumatol* 2016; **12**: 37–48.
2. Hamilton JA, Cook AD, Tak PP. Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases. *Nat Rev Drug Discov* 2016; **16**: 53–70.
3. Campbell IK, Rich MJ, Bischof RJ, Dunn AR, Grail D, Hamilton JA. Protection from collagen-induced arthritis in granulocyte-macrophage colony-stimulating factor-deficient mice. *J Immunol* 1998; **161**: 3639–44.
4. Greven DE, Cohen ES, Gerlag DM, et al. Preclinical characterisation of the GM-CSF receptor as a therapeutic target in rheumatoid arthritis. *Ann Rheum Dis* 2015; **74**: 1924–30.
5. Xu WD, Firestein GS, Taetle R, Kaushansky K, Zvaifler NJ. Cytokines in chronic inflammatory arthritis. II. Granulocyte-macrophage colony-stimulating factor in rheumatoid synovial effusions. *J Clin Invest* 1989; **83**: 876–82.
6. Hamilton JA, Tak PP. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. *Arthritis Rheum* 2009; **60**: 1210–21.
7. Achuthan A, Cook AD, Lee MC, et al. Granulocyte macrophage colony-stimulating factor induces CCL17 production via IRF4 to mediate inflammation. *J Clin Invest* 2016; **126**: 3453–66.
8. Haringman JJ, Gerlag DM, Zwinderman AH, et al. Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005; **64**: 834–8.
9. Tak PP, Smeets TJ, Daha MR, et al. Analysis of the synovial cell infiltrate in early rheumatoid synovial tissue in relation to local disease activity. *Arthritis Rheum* 1997; **40**: 217–25.
10. Mulherin D, Fitzgerald O, Bresnihan B. Synovial tissue macrophage populations and articular damage in rheumatoid arthritis. *Arthritis Rheum* 1996; **39**: 115–24.
11. Eylenstein R, Weinfurtner D, Hartle S, et al. Molecular basis of in vitro affinity maturation and functional evolution of a neutralizing anti-human GM-CSF antibody. *MAbs* 2016; **8**: 176–86.
12. Behrens F, Tak PP, Ostergaard M, et al. MOR103, a human monoclonal antibody to granulocyte-macrophage colony-stimulating factor, in the treatment of patients with moderate rheumatoid arthritis: results of a phase Ib/IIa randomised, double-blind, placebo-controlled, dose-escalation trial. *Ann Rheum Dis* 2015; **74**: 1058–64.
13. Buckley C, Simon Campos JA, Yakushin S, et al. A Phase IIb Dose-Ranging Study of Anti-GM-CSF with Methotrexate Treatment in Patients with Rheumatoid Arthritis (RA) and an Inadequate Response to Methotrexate. *Arthritis Rheum* 2018; **70 Suppl 9**: Abstract 1938.
14. Crotti C, Biggioggero M, Becciolini A, Agape E, Favalli EG. Mavrilimumab: a unique insight and update on the current status in the treatment of rheumatoid arthritis. *Expert Opin Investig Drugs* 2019; **28**: 573-81.
15. Conaghan PG, Cook AD, Hamilton JA, Tak PP. Therapeutic options for targeting inflammatory osteoarthritis pain. *Nat Rev Rheumatol* 2019; **15**: 355-63.
16. Hillen MR, Moret FM, van der Wurff-Jacobs K, et al. Targeting CD1c-expressing classical dendritic cells to prevent thymus and activation-regulated chemokine (TARC)-mediated T-cell chemotaxis in rheumatoid arthritis. *Scand J Rheumatol* 2017; **46**: 11–6.
17. Peterfy C, Strand V, Tian L, et al. Short-term changes on MRI predict long-term changes on radiography in rheumatoid arthritis: an analysis by an OMERACT Task Force of pooled data from four randomised controlled trials. *Ann Rheum Dis* 2017; **76**: 992–7.
18. Conaghan PG, Ostergaard M, Bowes MA, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. *Ann Rheum Dis* 2016; **75**: 1024–33.
19. Ostergaard M, Jacobsson LT, Schaufelberger C, et al. MRI assessment of early response to certolizumab pegol in rheumatoid arthritis: a randomised, double-blind, placebo-controlled phase IIIb study applying MRI at weeks 0, 1, 2, 4, 8 and 16. *Ann Rheum Dis* 2015; **74**: 1156–63.
20. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62**: 2569–81.
21. Ostergaard M, Edmonds J, McQueen F, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. *Ann Rheum Dis* 2005; **64 Suppl 1**: i3–7.
22. Kilani RT, Maksymowych WP, Aitken A, et al. Detection of high levels of 2 specific isoforms of 14-3-3 proteins in synovial fluid from patients with joint inflammation. *J Rheumatol* 2007; **34**: 1650–7.
23. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999; **10**: 223–32.

24. Peterfy CG, Olech E, DiCarlo JC, Merrill JT, Countryman PJ, Gaylis NB. Monitoring cartilage loss in the hands and wrists in rheumatoid arthritis with magnetic resonance imaging in a multi-center clinical trial: IMPRESS (NCT00425932). *Arthritis research & therapy* 2013; **15**: R44.
25. Conaghan PG, Emery P, Ostergaard M, et al. Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. *Ann Rheum Dis* 2011; **70**: 1968–74.
26. Ostergaard M, Emery P, Conaghan PG, et al. Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. *Arthritis Rheum* 2011; **63**: 3712–22.
27. Peterfy C, Emery P, Tak PP, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. *Ann Rheum Dis* 2016; **75**: 170–7.
28. Gupta A, Zecchin C, Fisheleva E, Layton M, Zamuner S. Exposure-Efficacy Analysis in DMARD Inadequate Response Rheumatoid Arthritis Patients Treated with GSK3196165 Along with Methotrexate. *Arthritis Rheum* 2018; **70 Suppl 9**: Abstract 2519.
29. Lee MC, Saleh R, Achuthan A, et al. CCL17 blockade as a therapy for osteoarthritis pain and disease. *Arthritis research & therapy* 2018; **20**: 62.
30. Burmester GR, McInnes IB, Kremer JM, et al. Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor alpha Monoclonal Antibody: Long-Term Safety and Efficacy in Patients With Rheumatoid Arthritis. *Arthritis Rheum* 2018; **70**: 679–89.

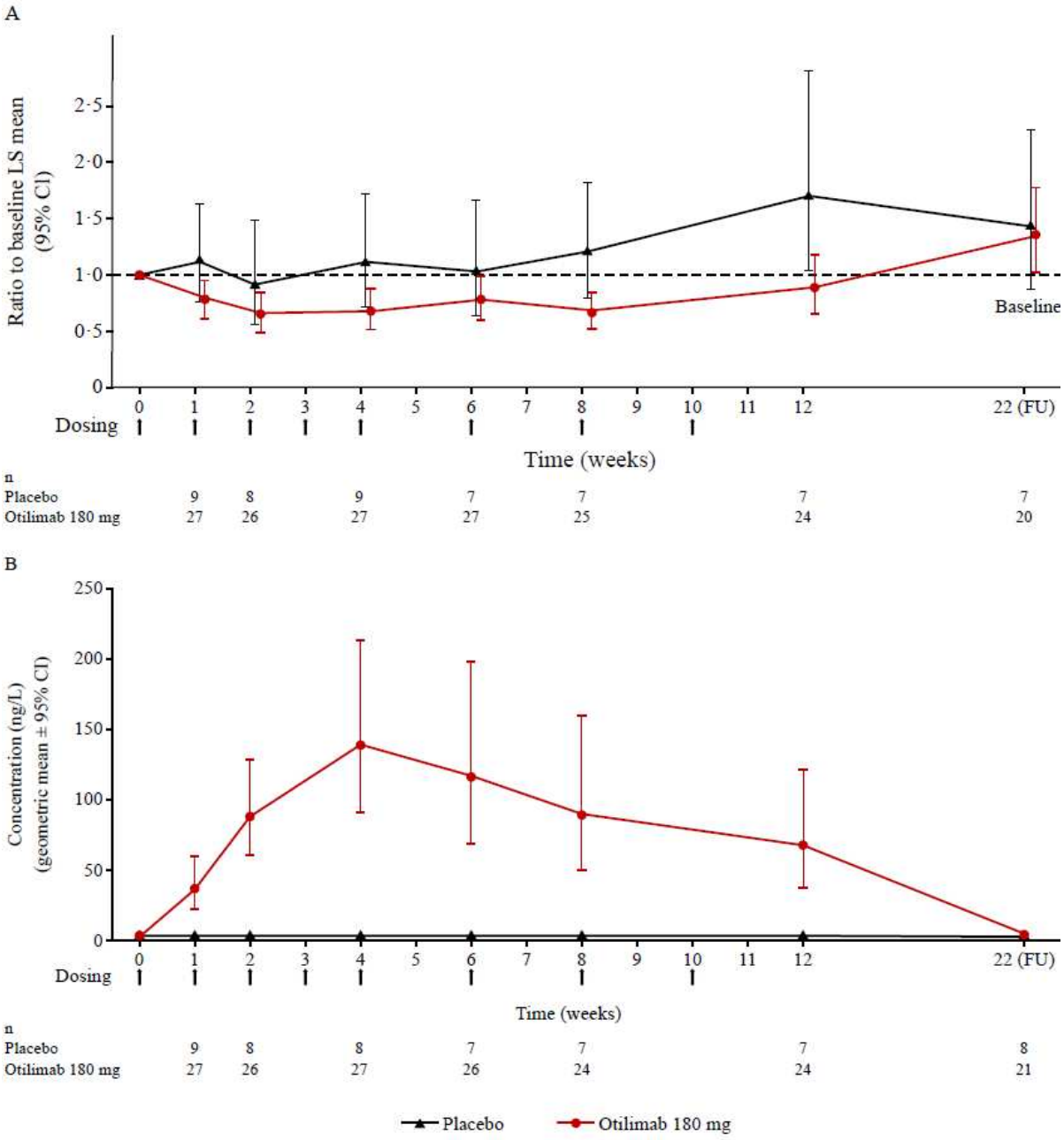
FIGURES AND TABLES

Figure 1. Patient disposition



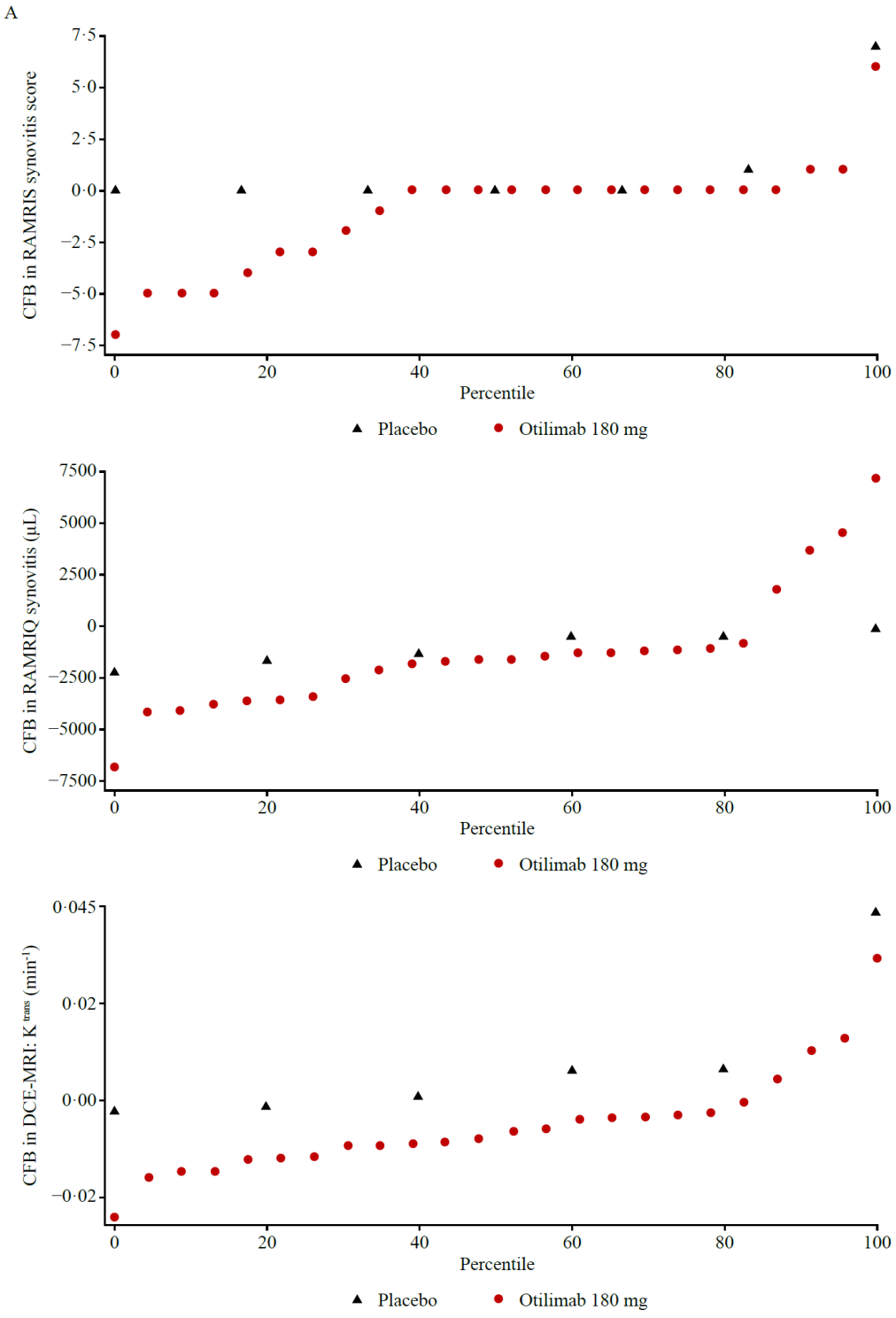
[a]Patients could be excluded for multiple reasons.

Figure 2. (A) CCL17 LS mean ratio to baseline over time (repeated measures analysis) and (B) GM-CSF/otilimab complex concentration (ng/L) geometric mean concentration over time (ITT population)



Dashed line represents baseline. CCL17, chemokine (C-C motif) ligand 17; CI, confidence interval; GM-CSF, granulocyte-macrophage colony-stimulating factor; FU, follow-up; ITT, intent-to-treat; LS, least squares.

Figure 3. (A) Cumulative probability plots of CFB at week 12 for RAMRIS synovitis score, RAMRIQ synovitis, and DCE-MRI: K^{trans}. (B) Synovitis maps of a week 12 ACR70 responder at baseline (left) and week 12 (right) following treatment. K^{trans} (min^{-1}) in joint overlaid on a bone rendering, with voxels colored as: 0–0·05 probably no disease (no colour), 0·05–0·1 low disease (green), 0·1–0·2 mild disease (yellow), 0·2+ high disease (red). (C) LS mean CFB in DAS28(CRP) over time (ITT population)



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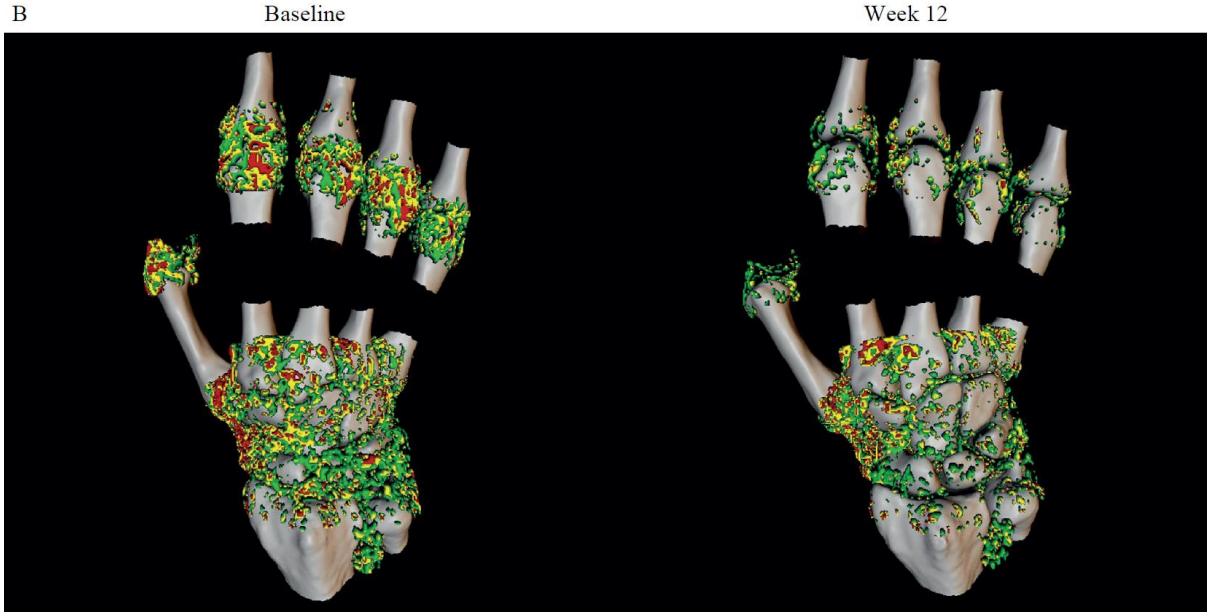
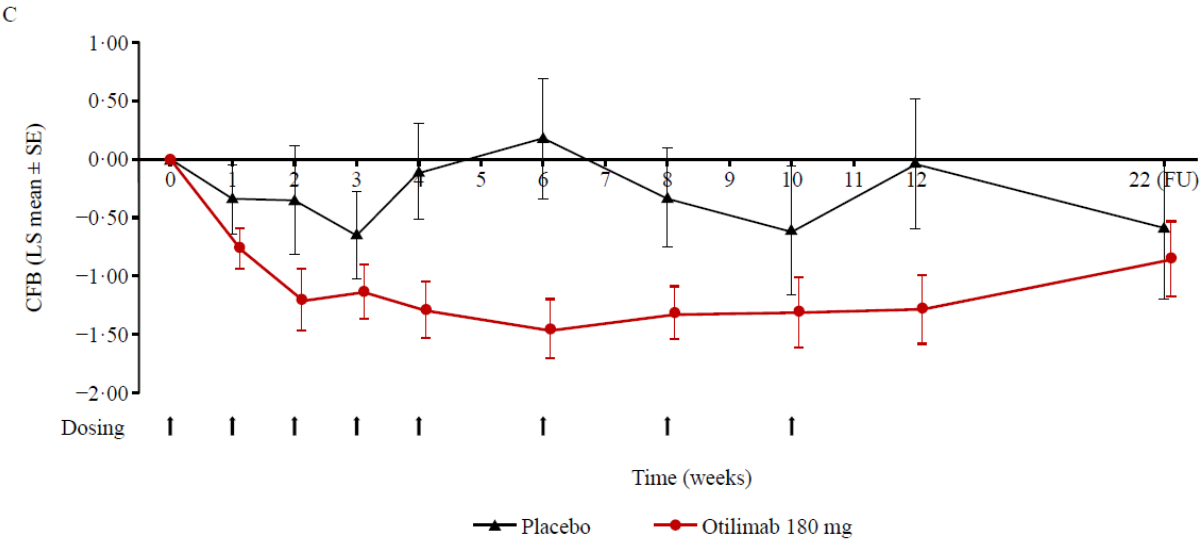


C



	DAS28(CRP)								
Week	1	2	3	4	6	8	10	12	22 (FU)
Placebo, n	9	8	10	9	6	7	7	7	7
LS mean CFB (SE)	−0·34 (0·301)	−0·35 (0·470)	−0·65 (0·381)	−0·11 (0·418)	0·18 (0·519)	−0·33 (0·423)	−0·61 (0·562)	−0·04 (0·559)	−0·60 (0·600)
Otilimab 180 mg, n	27	26	25	26	27	25	24	23	23
LS mean CFB (SE)	−0·77 (0·173)	−1·21 (0·266)	−1·14 (0·233)	−1·30 (0·247)	−1·46 (0·254)	−1·32 (0·231)	−1·32 (0·302)	−1·29 (0·300)	−0·86 (0·325)

ACR70, 70% improvement in American College of Rheumatology response; CFB, change from baseline; DAS28(CRP), disease activity score for 28 different joints with C-reactive protein; DCE-MRI, dynamic contrast enhanced magnetic resonance imaging; FU, follow-up; ITT, intent-to-treat; K^{trans}, rate of transfer of contrast agent from blood plasma to EES (extracellular extravascular space); LS, least squares; MRI, magnetic resonance imaging; RAMRIQ, rheumatoid arthritis magnetic resonance imaging quantitative assessment system; SE, standard error; RAMRIS, rheumatoid arthritis magnetic resonance imaging score.

Table 1. Baseline patient demographics and clinical characteristics (ITT population)

	Placebo (n=11)	Otilimab (n=28)
Patient demographics		
Age (years)		
Mean (SD)	50·3 (11·6)	59·1 (9·5)
Min, max	30, 75	40, 78
Female, n (%)	10 (91)	24 (86)
BMI (kg/m^2)		
Mean (SD)	31·5 (6·6)	30·4 (8·5)
Min, max	23·1, 45·1	17·8, 60·1
Ethnicity, n (%)		
Hispanic or Latino	6 (55)	15 (54)
Race, n (%)		
Black or African American	2 (18)	4 (14)
White	9 (82)	24 (86)
Clinical characteristics		
RA disease duration, n (%)		
≤2 years	2 (18)	6 (21)
>2 years	9 (82)	22 (79)
ACPA status, n (%)		
Positive	4 (36)	15 (54)
Missing	2 (18)	0 (0)
RF, n (%)		
Positive	4 (36)	17 (61)
Missing	1 (9)	0 (0)
DAS28(CRP), mean (SD)	6·4 (1·0)	6·3 (0·8)
CRP (mg/L), mean (SD)	17·0 (19·6)	14·5 (15·7)
SJC66, mean (SD)	25·1 (12·4)	25·4 (16·7)
TJC68, mean (SD)	35·5 (20·5)	36·4 (18·8)
HAQ-DI, mean (SD)	1·6 (0·6)	1·8 (0·5)
CDAI, mean (SD)	49·9 (16·7)	49·1 (13·1)
Pain VAS, mean (SD)	71·0 (17·0)	68·1 (17·8)
RAMRIS synovitis		
Mean (SD)	9·5 (5·2)	7·8 (4·3)
Score <5, n (%)	3 (27)	6 (21)
Prior DMARD, n (%)		
Hydroxychloroquine	0	2 (7)
Leflunomide	0	1 (4)
Azathioprine	0	1 (4)
Chloroquine	1 (9)	0
Adalimumab	0	1 (4)
Etanercept	0	1 (4)
Tofacitinib	0	1 (4)

ACPA, anti-cyclic citrullinated protein antibody; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28(CRP), disease activity score for 28 different joints with CRP value; DMARD, disease-modifying anti-rheumatic drug; HAQ-DI, Health Assessment Questionnaire – Disability Index; ITT, intent-to-treat; Max, maximum, Min, minimum; MTX, methotrexate; RA, rheumatoid arthritis; RAMRIS, rheumatoid arthritis magnetic resonance imaging score; RF, rheumatoid factor; SJC66, swollen joint count (66 joints); SD, standard deviation; TJC68, tender joint count (68 joints); VAS, visual analogue scale.

Table 2. CFB to week 12 in efficacy endpoints (ITT population)

Endpoint (week 12)	Placebo (n=11)	Otilimab (n=28)	Difference from placebo (95% CI)	p-value (difference from placebo)*
Clinical efficacy: CFB, LS mean (SE)				
DAS28(CRP)	−0·04 (0·56)	−1·29 (0·30)	−1·26 (−2·54, 0·03)	0·056
SJC28	–3·2 (3·30)	–7·5 (1·76)	–4·3 (–12·0, 3·3)	0·255
SJC66	−7·2 (5·36)	−12·6 (2·86)	−5·4 (−17·8, 7·0)	0·382
TJC28	1·3 (3·35)	–5·4 (1·81)	–6·7 (–14·5, 1·0)	0·086
TJC68	−0·1 (5·94)	−10·0 (3·22)	−9·9 (−23·6, 3·9)	0·154
Pain VAS	1·3 (9·68)	−14·7 (5·11)	−16·0 (−38·2, 6·3)	0·154
CRP (mg/L)	3·6 (3·50)	−3·6 (2·06)	−7·2 (−15·55, 1·25)	0·091
CDAI	−2·4 (7·35)	−16·7 (3·70)	−14·3 (−30·98, 2·45)	0·092
HAQ-DI	0·09 (0·21)	−0·30 (0·12)	−0·40 (−0·89, 0·10)	0·115
PtGA	–1·5 (9·38)	–14·3 (4·96)	–12·9 (–34·4, 8·7)	0·234
PhGA	2·1 (10·65)	–25·3 (5·26)	–27·4 (–51·6, –3·3)	0·027
MRI: CFB, LS mean (SE)				
RAMRIS synovitis	0·8 (1·17)	−1·3 (0·60)	−2·2 (−4·9, 0·5)	0·112
RAMRIQ synovitis (µL)	−912·3 (1405·77)	−1417·0 (671·54)	−504·8 (−3730·4, 2720·9)	0·749
DCE-MRI K^{trans} (min^{-1})	0·0081 (0·0055)	−0·0059 (0·0027)	−0·014 (−0·0266, −0·0013)	0·031
DCE-MRI *IRE* (μMs^{-1})	0·0004 (0·0003)	−0·0002 (0·0001)	−0·0006 (−0·0012, 0·0)	0·051
DCE-MRI *ME* (mM)	0·0357 (0·0282)	−0·0291 (0·0141)	−0·0648 (−0·1297, −0·0001)	0·050
Clinical efficacy: CFB, n (%)				
ACR20	1 (9)	9 (32)	23·1 (−1·2, 47·3)	–
ACR50	0	6 (21)	21·4 (6·2, 36·6)	–
ACR70	0	3 (11)	10·7 (−0·7, 22·2)	–
Good or moderate EULAR response criteria	2 (18)	13 (46)	28·2 (−1·1, 57·6)	–

*p-values were not calculated for binary efficacy endpoints due to low patient numbers in the placebo group; these data are summarised descriptively.

ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology response; CDAI, Clinical Disease Activity Index; CFB, change from baseline; CI, confidence interval; CRP, C-reactive protein; DAS28(CRP), disease activity score for 28 different joints with CRP value; DCE-MRI, dynamic contrast enhanced magnetic resonance imaging; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire – Disability Index; IRE, initial rate enhancement; ITT, intent-to-treat; K^{trans}, rate of transfer of contrast agent from blood plasma to extracellular extravascular space; LS, least squares; ME, maximal enhancement; MRI, magnetic resonance imaging; RAMRIQ, rheumatoid arthritis MRI quantification; RAMRIS, rheumatoid arthritis MRI scoring system; SE, standard error; SJC66, swollen joint count (66 joints); TJC68, tender joint count (68 joints); VAS, visual analogue scale.

Table 3. Summary of AEs up to week 22 (ITT population)

AEs, n (%) [#]*	Placebo (n=11)	Otilimab (n=28)
Any AE	4 (36) [8]	11 (39) [17]
Serious AEs	0	0
AEs leading to permanent discontinuation of study treatment	0	0
Treatment-related AEs	1 (9) [3]	3 (11) [4]
AEs of special interest (neutropaenia)	0	1 (4) [1]
Fatal serious AEs	0	0
All AEs		
Pain in extremity	2 (18) [4]	0
RA	2 (18) [4]	0
Musculoskeletal pain	0	1 (4) [1]
Upper respiratory tract infection	1 (9) [1]	1 (4) [1]
Laryngitis	0	1 (4) [1]
Nasopharyngitis	0	1 (4) [1]
Cough	0	2 (7) [3]
Asthma	0	1 (4) [1]
Alopecia	1 (9) [1]	0
Erythema	0	1 (4) [1]
Rosacea	0	1 (4) [1]
Seborrheic dermatitis	0	1 (4) [1]
Coronary artery disease	1 (9) [1]	0
Tachycardia	0	1 (4) [1]
Neutropaenia	0	1 (4) [1]
Nausea	0	1 (4) [1]
Fatigue	1 (9) [1]	0
Weight increased	0	1 (4) [1]
Headache	0	1 (4) [1]
Initial insomnia	0	1 (4) [1]

*n, number of patients with ≥1 event; #, number of individual occurrences.
AE, adverse event; ITT, intent-to-treat; RA, rheumatoid arthritis.