Efficacy, patient-reported outcomes, and safety of the anti-granulocyte macrophage colony-stimulating factor antibody otilimab (GSK3196165) in patients with rheumatoid arthritis: a randomised, phase 2b, dose-ranging study

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Summary

Background The human monoclonal antibody otilimab inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF), a key driver in immune-mediated inflammatory conditions. We aimed to evaluate the efficacy, safety, and key patient-reported outcomes related to pain in patients with active rheumatoid arthritis receiving otilimab.

Methods This phase 2b, dose-ranging, multicentre, placebo-controlled study was done at 64 sites across 14 countries. Patients aged 18 years or older with rheumatoid arthritis who were receiving stable methotrexate were randomly assigned (1:1:1:1:1:1) to subcutaneous placebo or otilimab 22·5 mg, 45 mg, 90 mg, 135 mg, or 180 mg, plus methotrexate, once weekly for 5 weeks, then every other week until week 50. The randomisation schedule was generated by the sponsor, and patients were assigned to treatment by interactive response technology. Randomisation was blocked (block size of six) but was not stratified. Investigators, patients, and the sponsor were blinded to treatment. An unblinded administrator prepared and administered the study drug. The primary endpoint was the proportion of patients who achieved disease activity score for 28 joints with C-reactive protein (DAS28-CRP) <2·6 at week 24. Patients who were not in the otilimab 180 mg group, without a good or moderate European League Against Rheumatism response (week 12) or with DAS28-CRP >3·2 (week 24) escaped to otilimab 180 mg. Patients who escaped were treated as non-responders in their original assigned group. Safety endpoints were incidence of adverse events and serious adverse events, infections, and pulmonary events. Efficacy and safety outcomes were assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT02504671.

Findings Between July 23, 2015, and Dec 29, 2017, 222 patients were randomly assigned (37 to each group). 86 (49%) of 175 escaped to otilimab 180 mg at week 12 and 57 (69%) of 83 at week 24. At week 24, the proportion of patients with DAS28-CRP <2·6 was two (5%) of 37 in the otilimab 22·5 mg group, six (16%) of 37 in the 45 mg group, seven (19%) of 37 in the 90 mg group, five (14%) of 37 in the 135 mg group, five (14%) of 37 in the 180 mg, and one (3%) of 37 in the placebo group. The largest difference was achieved with otilimab 90 mg (16·2%; odds ratio [OR] 8·39, 95% CI 0·98–72·14; p=0·053). Adverse events were reported pre-escape in 19–24 (51–65%) patients and post escape in 10–17 (40–61%) patients across otilimab dose groups and in 18 (49%) of 37 and 22 (67%) of 33 in the placebo group. The most common adverse event was nasopharyngitis: 3–9 (8–24%) in otilimab groups and one (3%) in the placebo group pre-escape and 1–3 (4–10%) in otilimab groups and seven (21%) in the placebo group post escape. Pre-escape serious adverse events were foot fracture (otilimab 45 mg); arthralgia, myocardial infarction, dizziness (otilimab 90 mg); oesophageal spasm, acute pyelonephritis (otilimab 22·5 mg), and uterine leiomyoma (otilimab 135 mg). Post-escape serious adverse events were ankle fracture (placebo) and rheumatoid arthritis (otilimab 135 mg). There were no deaths or pulmonary events of clinical concern, and rates of serious infection were low.

Interpretation Otilimab plus methotrexate was well tolerated and, despite not achieving the primary endpoint of DAS28-CRP remission, there were improvements compared with placebo in disease activity scores. Of note, patients reported significant improvement in pain and physical function, supporting further clinical development of otilimab in rheumatoid arthritis.

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Introduction

Many patients with rheumatoid arthritis have an inadequate response to currently available disease-modifying therapies,[1] with few achieving disease remission. Even when disease activity is reduced, many patients continue to have clinically significant pain, despite the availability of gold standard treatments that suppress disease-associated inflammation and damage.[2] Thus, there is an

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Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2000, and July 22, 2015, with the terms "rheumatoid arthritis" AND "mavrilimumab" OR "namilumab" OR "MOR103" OR "anti-GM-CSF" OR "anti-GMCSF", with no restriction on language. We identified four clinical trials: one proof-of-concept phase 1b/2a trial of otilimab (MOR103) and three phase 1/2/2a trials for mavrilimumab. Both drugs showed evidence of efficacy for targeting granulocyte-macrophage colony-stimulating factor (GM-CSF) or its receptor in patients with rheumatoid arthritis. Together with the strong preclinical evidence of a role for GM-CSF in the pathology of rheumatoid arthritis, and a need for alternative therapy options for rheumatoid arthritis, these findings supported the rationale to pursue the clinical development of otilimab, a monoclonal antibody that binds to and inhibits human GM-CSF. Furthermore, only one of the previous studies included assessment of patient-reported outcomes beyond Health Assessment Questionnaire-Disability Index (HAQ-DI). In the phase 1b/2a study of otilimab, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and pain Visual Analogue Scale (VAS) were also assessed; all patient-reported outcomes showed improvement following treatment with otilimab compared with placebo. The inclusion of a range of patient-reported outcomes in clinical studies is becoming increasingly important due to the chronic, long-term debilitating nature of the disease and ongoing disability for patients despite optimised clinical therapy. As such, a wider assessment of the impact of anti-GM-CSF treatment on patient-reported outcomes in rheumatoid arthritis was required.

Added value of this study

To our knowledge, this is the first clinical trial in the field of rheumatology with a novel study design offering an automated and blinded escape to a higher dose of otilimab to patients with rheumatoid arthritis who had not obtained a meaningful benefit from their randomised treatment, with the aim to achieve an optimised treat-to-target dosing regimen. We observed dose-related and meaningful clinical benefit with otilimab in patients with an inadequate response to methotrexate. Otilimab treatment led to rapid reduction in tender and swollen joint counts and hence Clinical Disease Activity Index scores. This is also (to our knowledge) the first clinical trial assessing an anti-GM-CSF antibody in rheumatoid arthritis to include a wide panel of patient-reported outcomes: HAQ-DI, pain VAS, short-form health survey and components, FACIT-Fatigue, Brief Fatigue Inventory—Question 3, and Patient's Global Assessment of Arthritis Disease Activity. We observed substantial improvement in a range of these patient-reported outcomes, particularly in pain scores. Otilimab treatment was well tolerated and no significant unexpected safety findings were observed.

Implications of all the available evidence

The results of this study build on the existing data and support a positive benefit:risk profile of treatment with otilimab in active rheumatoid arthritis and provide a basis for further clinical development. The temporal changes in pain compared with the temporal changes in disease activity, including acute phase reactants (C-reactive protein), suggest a particular role for GM-CSF inhibition in pain response in active rheumatoid arthritis.

impetus to investigate new treatments in rheumatoid arthritis that target pain as well as inflammation and damage, and explore whether disease activity, clinical remission, and pain are always associated or can be dissociated mechanistically and clinically.

In pathological conditions, granulocyte-macrophage colony-stimulating factor (GM-CSF)[3] is a key driver of inflammation, pain, and tissue damage in a range of immune-mediated disease states.[3–5] Concentrations of GM-CSF are increased in the synovial tissue of some patients with rheumatoid arthritis,[6,7] and GM-CSF augments myeloid cell activation,[8] leading to production of inflammatory cytokines, such as interleukin (IL)-6, IL-1, tumour necrosis factor (TNF) and chemokine (C-C motif) ligand 17 (CCL17), which are associated with pain and can result in severe tissue damage.[3,9] Mechanistic studies indicate that GM-CSF is involved in the development of pain-like behaviour in mouse models of inflammatory pain and arthritis,[5,10] and a role for GM-CSF in sensitising sensory nerves was shown in a mouse sarcoma model.[11] Therefore, anti-GM-CSF agents could have a key role in treating inflammation and pain in multiple conditions, including rheumatoid arthritis.[8,10]

Otilimab (also known as GSK3196165, MOR103, and MOR04357) is a high-affinity recombinant human monoclonal IgG1 antibody that specifically binds to human GM-CSF, inhibiting its activity.[12] Phase 1 and 2 clinical trials in patients with rheumatoid arthritis indicated that inhibition of GM-CSF signalling by human monoclonal antibodies, including otilimab, leads to clinical benefit with a reduction in disease activity.[13–16] We aimed to evaluate the efficacy, safety, and key patient-reported outcomes related to pain in patients with active rheumatoid arthritis receiving otilimab.

Methods

Study design and participants

This randomised, phase 2b, dose-ranging, multicentre, double-blind, parallel-group, placebo-controlled study (appendix p 7) was done at 64 sites across 14 countries (appendix p 2). Patients aged 18 years or older, with a clinical diagnosis of rheumatoid arthritis according to American College of Rheumatology (ACR)–European

See Online for appendix

League Against Rheumatism (EULAR) 2010 classification criteria,[17] receiving methotrexate and with a disease duration of at least 12 weeks were eligible. Patients were required to have Functional Class I, II or III (1992 ACR Classification of Functional Status in rheumatoid arthritis),[18] swollen joint count in 66 joints (SJC66) of 4 or more, tender joint count in 68 joints (TJC68) of 4 or more at screening and at day 1, disease activity score for 28 joints with C-reactive protein (DAS28-CRP) of 3·2 or more at screening or DAS28 with erythrocyte sedimentation rate (DAS28-ESR) of 3·2 or more at day 1. For pulmonary safety, patients were required to have diffusing capacity or transfer factor of the lung for carbon monoxide (D_{LCO}) of 60% or more and forced expiratory volume in 1 second (FEV_1) of 70% or more predicted at screening. Patients with a history of other inflammatory rheumatological or autoimmune disorders, clinically significant or unstable persistent cough, or unexplained dyspnoea were excluded. Full eligibility criteria are provided in the appendix (pp 2–5).

This study was done in accordance with the International Council for Harmonisation Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki.[19] Study ethical approval was obtained at all sites; the first ethical approval was obtained on May 22, 2015 for investigational sites in Canada (Schulman Associates Institutional Review Board). Key protocol amendments are listed in the appendix (p 2). All patients provided written informed consent. An independent data monitoring committee monitored the study.

Randomisation and masking

Patients were randomly assigned (1:1:1:1:1:1) to six treatment groups: placebo or otilimab 22·5 mg, 45 mg, 90 mg, 135 mg, or 180 mg. Randomisation was blocked (block size six). Patients were assigned to treatment using central randomisation according to a schedule generated by the study sponsor using validated software. Randomisation numbers were assigned using an interactive response technology system. Randomisation was not stratified. Patient recruitment was done by study investigators. To ensure blinding of treatment assignments during the study, an unblinded administrator (study coordinator or nurse) prepared and administered the study drug. Further information on blinding is provided in the appendix (p 5).

Procedures

Treatments were administered subcutaneously once weekly for the first 5 weeks, then every other week from week 6 until week 50. The rationale for dose selection and guidelines for treatment withdrawal or interruption are provided in the appendix (pp 5–6). A 12-week safety follow-up period began after the final dose. All patients continued to receive methotrexate 7·5–25 mg/week and folic (or folinic) acid 5 mg/week or more during the treatment period.

Patients who were not assigned to otilimab 180 mg escaped in an automated blinded procedure to otilimab 180 mg if they did not achieve a good or moderate EULAR response at week 12 or had DAS28-CRP of more than 3·2 at week 24. Any patients who did not achieve a EULAR good or moderate response at week 36 were withdrawn from treatment at the next visit in an automated procedure.

Efficacy outcomes, Health Assessment Questionnaire-Disability Index (HAQ-DI) score, pain Visual Analogue Scale (VAS), and Patient's Global Assessment of Arthritis Disease Activity (PtGA) were assessed at screening, baseline (day 1), weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, and at follow-up (week 62). Brief Fatigue Inventory–Question 3 (BFI-Q3), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and 36-item short-form health survey (SF-36) were assessed at baseline, weeks 4, 12, 24, 36, and 52, and at follow-up. Blood samples for pharmacokinetic and biomarker outcomes were taken at baseline, weeks 1, 2, 4, 6, 8, 12, 24, 36, and 52, and at follow-up; additional blood samples for pharmacokinetic analysis only were taken at weeks 16 and 20.

Safety parameters were monitored throughout the study until follow-up, including monitoring of adverse events, serious adverse events, adverse events of special interest, infections, and immunogenicity. The following pulmonary assessments were done at screening, day 1, week 12, 24, 36, and 52, and follow-up: chest x-ray at screening, cough, Borg dyspnoea questionnaire, lung auscultation, pulse oximetry, spirometry (FEV_1, forced vital capacity), and D_{LCO}. Laboratory monitoring for haematology and chemistry was done at screening, week 2, 4, 8, 12, 16, 20, 24, 32, 42, and at follow-up; urinalysis was done at the same timepoints, excluding week 2; cholesterol, triglycerides, and lipoproteins were assessed at screening, week 12, and 24, and follow-up.

Outcomes

The primary endpoint was the proportion of patients who achieved DAS28-CRP remission (DAS28-CRP <2·6) at week 24.

Secondary endpoints were change from baseline in DAS28-CRP at week 12 and all other assessment timepoints; proportion of patients who achieved DAS28-CRP remission at all timepoints; time to first DAS28-CRP remission; ACR20, ACR50, and ACR70 and good or moderate EULAR response rate at all timepoints; index-based and Boolean-based ACR–EULAR remission rates and CDAI remission rate at all timepoints; change from baseline in SJC66, TJC68, Simple Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI); change from baseline in patient-reported outcomes at all time points using HAQ-DI score, pain VAS, physical and mental component of SF-36, FACIT-Fatigue, and BFI-Q3. Pharmacokinetics was assessed as a secondary objective; endpoints were: otilimab serum concentration and

evaluation of target engagement biomarkers, including free soluble GM-CSF and soluble GM-CSF complexed to otilimab (GM-CSF–otilimab complex).

Safety endpoints were incidence of adverse events and serious adverse events, infections, and pulmonary events. Any new or clinically significant pulmonary abnormalities (eg, increased dyspnoea, unexplained and persistent cough, or >15% relative decrease in D_{LCO} from baseline) were referred to a pulmonologist for further assessment to identify any cases of pulmonary alveolar proteinosis.

Statistical analysis

On the basis of a Fisher's exact test, a planned sample size of 35 patients per group provided around 90% power to detect a difference of 30% in the proportion of patients achieving DAS28-CRP remission at week 24 between each otilimab dose and placebo at the 2-sided α of 0·05 (33% *vs* 3%). The difference of 30% between groups was based on the expected clinical profile for otilimab, and the predicted placebo rate of 3% was based on the literature review of current therapies presenting DAS28-CRP remission results. The efficacy and safety population was the intention-to-treat population, defined as all randomly assigned patients who received at least one dose of study drug. The pharmacokinetic population was all randomly assigned patients who received at least one dose of otilimab and had at least one quantifiable otilimab concentration available.

Binary endpoints, including the primary endpoint, were assessed using a logistic regression model adjusted for treatment group and appropriate baseline scores. A non-responder imputation was used for patients with missing efficacy data and those who escaped to the otilimab 180 mg dose.

All continuous efficacy endpoints, including patient-reported outcomes, were analysed using mixed model repeated measures with fixed effects for treatment group and baseline value. Change from baseline will be missing at visits with missing post-baseline values, and all patients who escaped to otilimab 180 mg were set to missing post escape. The serum otilimab and target engagement biomarker concentrations were summarised by descriptive statistics by treatment group and visit up to week 52. A post-hoc analysis was done to evaluate the percentage of patients with pain improvement of at least the minimal clinically important difference (10 mm difference on 100 mm VAS).

Two interim analyses were planned. Interim 1 was done when 90 patients completed week 4 and interim 2 when 90 completed week 12 to evaluate whether to terminate the study on the basis of the dose response association in change in DAS28-CRP from baseline. Interim 2 also evaluated the predictive probabilities of observing a 25% difference at week 24 in DAS28-CRP remission and whether there was a need to terminate individual dose treatment groups. Following the interim analyses, the study was not stopped and there were no changes made to the treatment groups.

All analyses were done using SAS version 9.3. This study is registered with ClinicalTrials.gov, NCT02504671.

Role of the funding source

This study was sponsored by GlaxoSmithKline (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 in the study, contributed to writing or reviewing of the report, and approved the final submitted version. The corresponding author had the final responsibility to submit for publication.

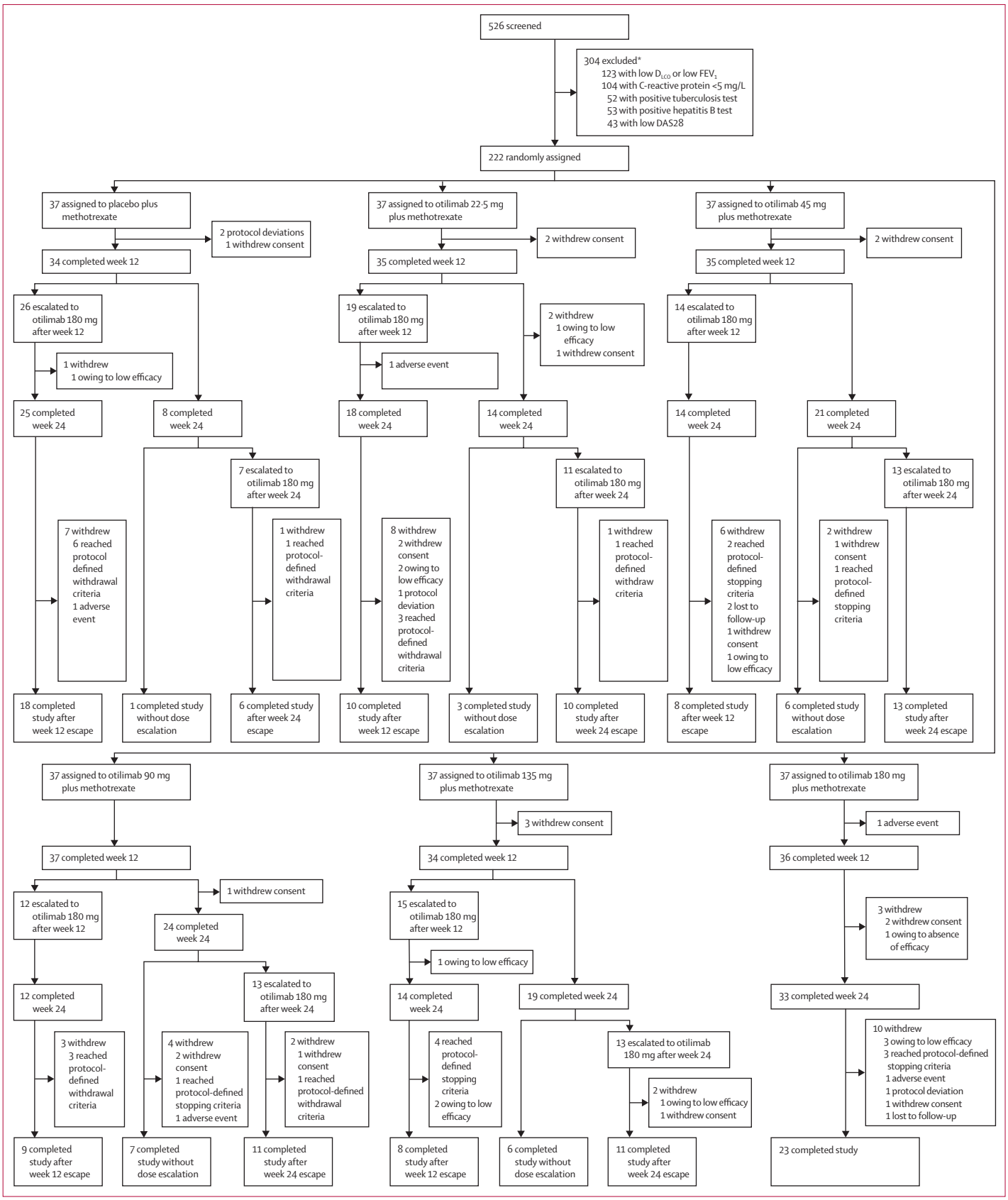
Results

The study began on July 23, 2015, and was completed on Dec 29, 2017. Of 526 patients with rheumatoid arthritis who were screened, 222 met the inclusion criteria and were randomly assigned. A large proportion of patients escaped to the 180 mg dose at week 12 (figure 1). No protocol violations affected the interpretation of the study results (appendix p 13).

Baseline demographics, disease activity characteristics and patient-reported outcome measures were balanced across treatment groups (table 1), other than a high proportion of female patients (180 [81%] of 222), which is typical for a rheumatoid arthritis population, and a slight imbalance in CRP, which was higher in the otilimab 22·5 mg group compared with other groups. The mean age was 50·5 years (SD 11·3). Although the inclusion criteria allowed moderate-to-severe rheumatoid arthritis, baseline disease characteristics were indicative of severe rheumatoid arthritis—mean DAS28-CRP was 6·19 (0·84) and mean disease duration ranged from 5·1 years (SD 6·4; 45 mg group) to 7·7 years (7·1; 180 mg group). Mean CDAI was 44·31 (SD 12·82). Mean pain VAS score was 67·0 (18·49); mean HAQ-DI score was 1·76 (0·56), and mean FACIT-Fatigue score was 25·7 (9·82).

At week 24, DAS28-CRP <2·6 remission rates were consistently higher for all otilimab dose groups versus placebo, but none were statistically significant. The difference to placebo in DAS28-CRP remission rate was 2·7–16·2%; the biggest difference was with otilimab 90 mg (16·2%; odds ratio [OR] 8·39, 95% CI 0·98–72·14; p=0·053; figure 2A). The initial reduction in DAS28-CRP

Figure 1: **Patient disposition**
DAS28=Disease Activity Score for 28 joints. D_{LCO}=diffusing capacity or transfer factor of the lung for carbon dioxide. EULAR=European League Against Rheumatism. FEV_1=forced expiratory volume in 1 second. *Patients could be excluded for multiple reasons.


526 screened
304 excluded*
123 with low D_{LCO} or low FEV_1
104 with C-reactive protein <5 mg/L
52 with positive tuberculosis test
53 with positive hepatitis B test
43 with low DAS28
222 randomly assigned
37 assigned to placebo plus methotrexate
2 protocol deviations
1 withdrew consent
34 completed week 12
26 escalated to otilimab 180 mg after week 12
1 withdrew
1 owing to low efficacy
25 completed week 24
8 completed week 24
7 escalated to otilimab 180 mg after week 24
7 withdrew
6 reached protocol defined withdrawal criteria
1 adverse event
1 withdrew
1 reached protocol-defined withdrawal criteria
18 completed study after week 12 escape
1 completed study without dose escalation
6 completed study after week 24 escape
37 assigned to otilimab 22·5 mg plus methotrexate
2 withdrew consent
35 completed week 12
19 escalated to otilimab 180 mg after week 12
2 withdrew
1 owing to low efficacy
1 withdrew consent
1 adverse event
18 completed week 24
14 completed week 24
8 withdrew
2 withdrew consent
2 owing to low efficacy
1 protocol deviation
3 reached protocol-defined withdrawal criteria
11 escalated to otilimab 180 mg after week 24
1 withdrew
1 reached protocol-defined withdraw criteria
10 completed study after week 12 escape
3 completed study without dose escalation
10 completed study after week 24 escape
37 assigned to otilimab 45 mg plus methotrexate
2 withdrew consent
35 completed week 12
14 escalated to otilimab 180 mg after week 12
14 completed week 24
21 completed week 24
13 escalated to otilimab 180 mg after week 24
6 withdrew
2 reached protocol-defined stopping criteria
2 lost to follow-up
1 withdrew consent
1 owing to low efficacy
2 withdrew
1 withdrew consent
1 reached protocol-defined stopping criteria
8 completed study after week 12 escape
6 completed study without dose escalation
13 completed study after week 24 escape
37 assigned to otilimab 90 mg plus methotrexate
37 completed week 12
1 withdrew consent
12 escalated to otilimab 180 mg after week 12
24 completed week 24
13 escalated to otilimab 180 mg after week 24
12 completed week 24
3 withdrew
3 reached protocol-defined withdrawal criteria
4 withdrew
2 withdrew consent
1 reached protocol-defined stopping criteria
1 adverse event
2 withdrew
1 withdrew consent
1 reached protocol-defined withdrawal criteria
9 completed study after week 12 escape
7 completed study without dose escalation
11 completed study after week 24 escape
37 assigned to otilimab 135 mg plus methotrexate
3 withdrew consent
34 completed week 12
15 escalated to otilimab 180 mg after week 12
1 owing to low efficacy
14 completed week 24
19 completed week 24
4 reached protocol-defined stopping criteria
2 owing to low efficacy
13 escalated to otilimab 180 mg after week 24
2 withdrew
1 owing to low efficacy
1 withdrew consent
8 completed study after week 12 escape
6 completed study without dose escalation
11 completed study after week 24 escape
37 assigned to otilimab 180 mg plus methotrexate
1 adverse event
36 completed week 12
3 withdrew
2 withdrew consent
1 owing to absence of efficacy
33 completed week 24
10 withdrew
3 owing to low efficacy
3 reached protocol-defined stopping criteria
1 adverse event
1 protocol deviation
1 withdrew consent
1 lost to follow-up
23 completed study

	Placebo (n=37)	Otilimab				
		22·5 mg (n=37)	45 mg (n=37)	90 mg (n=37)	135 mg (n=37)	180 mg (n=37)
Age, years	50·0 (11·3)	48·4 (11·3)	52·8 (12·2)	52·7 (11·3)	47·1 (10·0)	52·3 (10·8)
Sex						
Female	28 (76%)	30 (81%)	33 (89%)	27 (73%)	33 (89%)	29 (78%)
Male	9 (24%)	7 (19%)	4 (11%)	10 (27%)	4 (11%)	8 (22%)
Rheumatoid arthritis diagnosis, years	6·2 (7·9)	6·3 (6·8)	5·1 (6·4)	6·1 (6·0)	6·9 (5·6)	7·7 (7·1)
Anti-cyclic citrullinated protein antibody positive	28 (76%)	24 (65%)	24 (65%)	23 (62%)	28 (76%)	30 (81%)
Rheumatoid factor positive	28 (76%)	26 (70%)	27 (73%)	21 (57%)	22 (59%)	30 (81%)
DAS28-CRP	6·2 (0·8)	6·4 (0·8)	6·1 (0·7)	6·2 (0·8)	6·3 (0·9)	6·0 (0·9)
Simplified Disease Activity Index (0-86)	47·4 (13·3)	48·0 (12·9)	45·2 (12·0)	46·5 (13·0)	48·2 (14·6)	44·4 (14·0)
Clinical Disease Activity Index (0-76)	45·7 (13·5)	45·2 (11·8)	42·8 (12·1)	44·5 (12·6)	45·3 (13·5)	42·5 (13·9)
Tender joint count for 68 different joints	28·5 (13·6)	27·9 (12·1)	26·1 (14·1)	28·8 (14·8)	30·1 (14·8)	25·3 (12·4)
Swollen joint count for 66 different joints	18·5 (9·3)	17·7 (8·5)	17·2 (8·9)	18·3 (10·1)	18·9 (10·2)	18·9 (10·1)
Pain (100 mm VAS)	66·1 (16·7)	71·2 (15·8)	70·1 (17·3)	65·8 (20·4)	67·1 (19·3)	61·6 (20·6)
Patient's global assessment of arthritis (100 mm VAS)	66·0 (15·6)	72·5 (14·2)	71·6 (14·9)	68·2 (17·6)	69·6 (17·0)	63·2 (16·6)
Physician's global assessment of arthritis (100 mm VAS)	64·2 (11·9)	67·5 (10·3)	67·1 (15·9)	65·9 (18·6)	67·2 (15·4)	64·1 (15·7)
FACIT-Fatigue	24·7 (8·6)	25·9 (9·1)	26·5 (9·2)	25·1 (9·9)	24·3 (9·6)	27·6 (12·4)
Brief Fatigue Inventory-Question 3	6·5 (1·9)	6·5 (2·2)	6·5 (2·0)	6·7 (2·1)	6·6 (1·9)	5·8 (2·5)
Health Assessment Questionnaire-Disability Index	1·8 (0·6)	1·7 (0·5)	1·9 (0·4)	1·3 (0·5)	1·8 (0·6)	1·6 (0·7)
Short Form (36) Health Survey (Mental Score)	42·5 (9·4)	41·8 (9·9)	42·3 (9·4)	40·7 (10·4)	41·4 (12·6)	41·3 (13·1)
Short Form (36) Health Survey (Physical Score)	29·0 (5·6)	28·6 (6·1)	28·6 (7·0)	30·2 (6·6)	28·5 (7·0)	31·8 (7·9)
High sensitivity C-reactive protein, median (range), mg/mL	12·9 (2–66)	19·5 (3–135)	14·7 (1–158)	13·7 (1–99)	15·6 (1–261)	12·7 (2–103)
Previous DMARDs						
Methotrexate	36 (97%)	37 (100%)	37 (100%)	37 (100%)	37 (100%)	36 (97%)
Sulfasalazine	5 (14%)	6 (16%)	3 (8%)	8 (22%)	9 (24%)	6 (16%)
Leflunomide	1 (3%)	4 (11%)	3 (8%)	3 (8%)	8 (22%)	4 (11%)
Hydroxychloroquine	2 (5%)	2 (5%)	4 (11%)	1 (3%)	3 (8%)	2 (5%)
Azathioprine	1 (3%)	0	0	1 (3%)	0	0
Chloroquine	2 (5%)	2 (5%)	0	1 (3%)	3 (8%)	1 (3%)
Adalimumab	0	0	0	1 (3%)	0	0
Oral glucocorticoids						
Oral glucocorticoid use	15 (41%)	24 (65%)	20 (54%)	22 (59%)	21 (57%)	22 (59%)
Oral glucocorticoid dose, prednisolone equivalent, mg/day	6·4 (2·1)	6·0 (2·9)	6·8 (2·6)	6·8 (3·0)	5·9 (3·2)	5·9 (2·7)

Data are n (%) or mean (SD), unless otherwise specified. DAS28-CRP=Disease activity score for 28 different joints with C reactive protein value. DMARDs=disease-modifying antirheumatic drugs. FACIT=Functional Assessment of Chronic Illness Therapy VAS=Visual Analogue Scale.

Table 1: **Baseline patient demographics and clinical characteristics**

was rapid for all otilimab dose groups, followed by a slower rate of improvement from week 6 to 12. On the basis of the patients originally assigned to otilimab 180 mg, the improvement in DAS28-CRP reached a plateau between weeks 12 and 24 (figure 2B). A post-hoc analysis indicated that, at week 24, the proportion of patients achieving DAS28-CRP low disease activity (≤3·2) generally increased with increasing dose (appendix p 14).

There was a significant difference in DAS28-CRP mean change from baseline between the 180 mg group and placebo at week 12 (–1·27, 95% CI –1·91 to 0·63; p=0·0001) and week 24 (–1·82, –2·75 to –0·89; p=0·0002; appendix pp 15–16). Dose-response modelling for change from baseline in DAS28-CRP at week 12 predicted DAS28-CRP response for otilimab 180 mg was –1·19 (95% CI –1·75, –0·63). Time to first DAS28-CRP remission was shortest in the otilimab 90 mg dose group (mean 8·91 weeks, SD 4·022).

Given that a substantial number of patients had escaped to the 180 mg dose of otilimab at week 12 and that target saturation was not achieved after week 8, subsequent analyses included data up to and including the week 12 timepoint. Secondary endpoint data for all timepoints up to week 12 are provided in the appendix (pp 17–30).

At week 12, significantly more patients receiving any otilimab dose achieved an ACR20 response versus placebo, and significantly more achieved an ACR50 response with

the 45 mg and 135 mg doses versus placebo; there was no significant difference between placebo and otilimab groups for ACR70 response (figure 2C). At week 12, a larger proportion of patients had a good or moderate EULAR response in the otilimab groups versus placebo (appendix p 19). The highest proportion of patients with a good or moderate EULAR response was in the otilimab 180 mg group (28 [76%] of 37; difference versus placebo 54·1%, 95% CI 34·9 to 73·2; OR 10·93, 95% CI 3·68 to 32·51; p<0·0001). CDAI remission rate at week 12 was highest in the otilimab 90 mg dose group (four [11%] of 37; difference versus placebo 8·1% [95% CI –3·2 to 19·4]; appendix pp 19–20). Index-based (SDAI ≤3·3) and Boolean-based ACR–EULAR remission rates could not be assessed due to low numbers of responders.

There was a rapid and substantial improvement in SJC66, TJC68, CDAI (appendix p 8), and SDAI (appendix p 24) in all otilimab dose groups versus placebo. For SJC66, there was a significant difference versus placebo in least-squares mean change from baseline to week 12 in the 180 mg group (–7·54, 95% CI –11·78 to –3·30; p=0·0006) and the 90 mg group (–5·63, 95% CI –9·85 to –1·41; p=0·0092). For TJC68, the biggest difference versus placebo in least-squares mean change from baseline to week 12 was in the 180 mg group (–8·91, 95% CI –14·72 to 3·10; p=0·0028). The greatest change in CDAI from baseline at week 12 was observed in the otilimab 180 mg dose group, with a difference versus placebo of –16·63 (95% CI –23·97 to –9·30; p<0·0001). For SDAI, the biggest difference versus placebo in least-squares mean change from baseline to week 12 was in the 180 mg group (–16·86, 95% CI –24·39 to –9·32; p<0·0001). A sustained reduction in CRP concentrations from baseline to week 12 of around 50% was evident in otilimab dose groups of 45 mg and above, although these changes were not statistically significant versus placebo (appendix p 8).

Early, consistent, and sustained (up to week 12) improvements from baseline were observed in patient-reported outcome measures (figure 3; appendix pp 9–10). By week 4 there was a significant difference in least-squares mean change from baseline in patient's assessment of pain (VAS) versus placebo for most doses of otilimab (except for the 22·5 mg and 135 mg doses). At week 12 there was a significant difference in pain versus placebo for all doses except for the 22·5 mg dose; the largest differences versus placebo were in the 90 mg dose group (–18·18, 95% CI –28·35 to –8·01; p=0·0005) and the 180 mg dose group (–17·94, 95% CI –28·18 to –7·70; p=0·0007; figure 3A). A post-hoc analysis revealed that overall, otilimab treatment

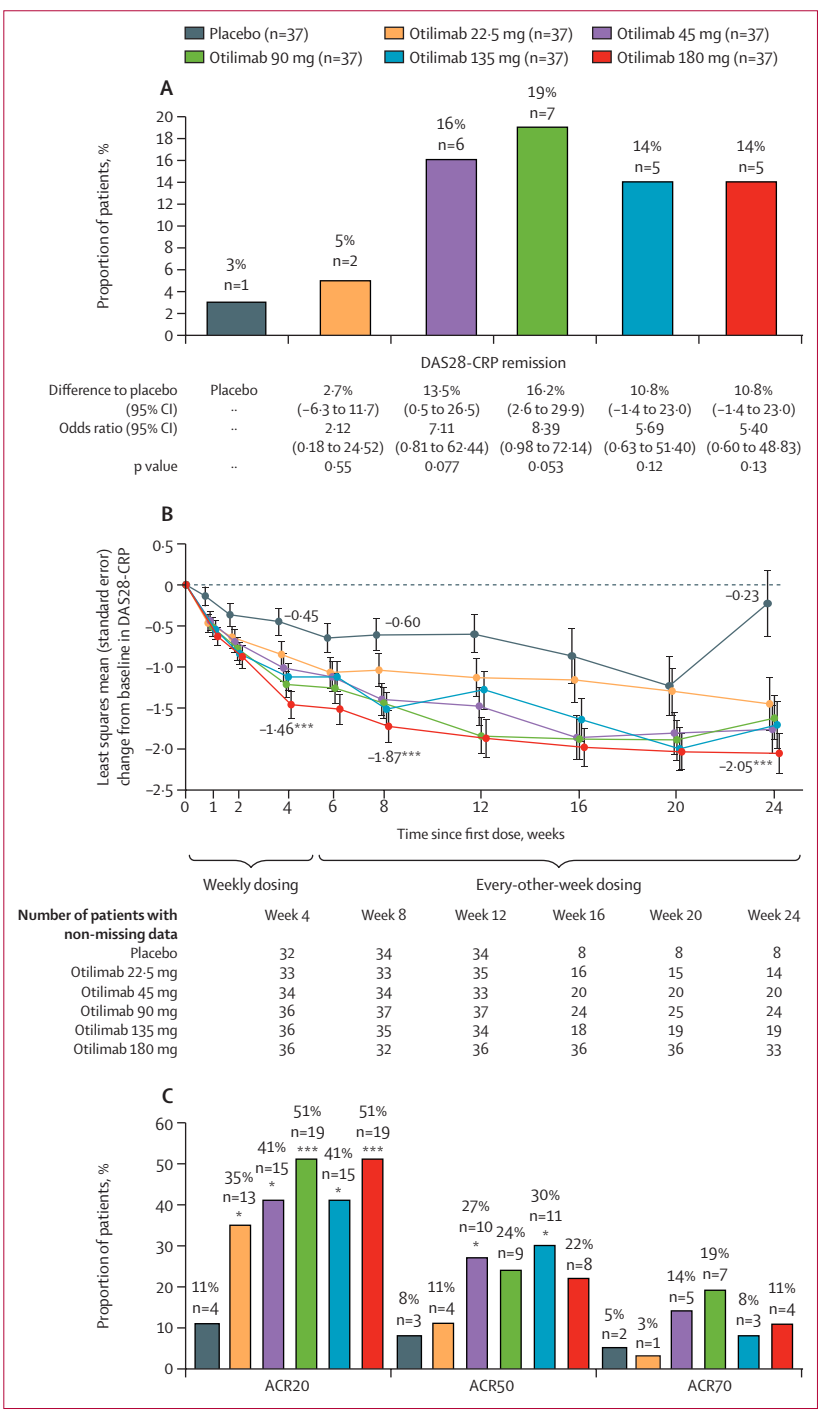


Figure 2: **Clinical efficacy of otilimab versus placebo**
(A) DAS28-CRP <2·6 remission rate at week 24. (B) DAS28-CRP change from baseline over 24-week treatment period (observed results). (C) ACR responses at week 12 (intention-to-treat population). DAS28-CRP <2·6 remission rate at week 24 and ACR response at week 12 (binary endpoints) were analysed using logistic regression model by visit with fixed effects for treatment group and appropriate baseline score; non-responder imputation was used for patients with missing efficacy data and those who escaped to otilimab 180 mg dose. DAS28-CRP change from baseline over the 24-week treatment period (continuous endpoint) was analysed using repeated measures analysis adjusted for DAS28-CRP baseline score, treatment group, visit and treatment group by visit, and baseline by visit interactions. Patients who escaped to otilimab 180 mg at week 12 were set to missing. Data post-week 24 were excluded due to the quantity of missing data. Values on graph are least-squares mean change from baseline at week 4, week 12, and week 24. ACR=American College of Rheumatology. CRP=C-reactive protein. DAS28-CRP=Disease Activity Score for 28 different joints with CRP. *p<0·05. **p<0·02. ***p<0·01.

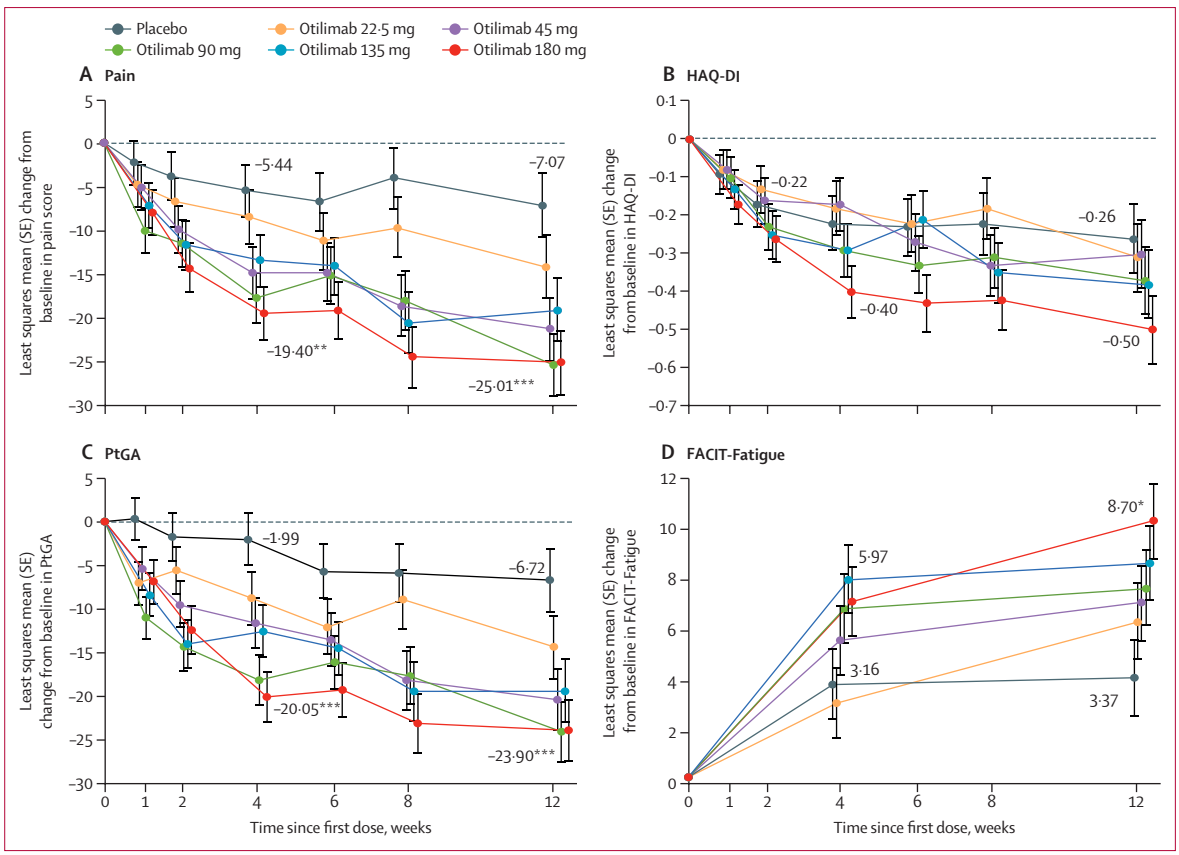


Figure 3: **Change from baseline in patient-reported outcome measures**

Least-squares mean change from baseline in pain (A), HAQ-DI (B), PtGA (C), and FACIT-Fatigue over time (D; intention-to-treat population). Repeated measures analysis adjusted for baseline, treatment group, visit and treatment group by visit and baseline by visit interactions. Values on graph are least-squares mean change from baseline at week 4 and week 12. For FACIT-Fatigue, higher scores indicate better quality of life. Pain and PtGA were assessed by VAS. FACIT=Functional Assessment of Chronic Illness Therapy. HAQ-DI=Health Assessment Questionnaire-Disability Index. PtGA=Patient's Global Assessment of Arthritis Disease Activity. SE=standard error. VAS=Visual Analogue Scale. *p<0·05. **p<0·01. ***p<0·001.

was associated with a larger proportion of patients with pain improvement of a 10 mm or more difference on 100 mm VAS (minimal clinically important difference) versus placebo, with the largest difference versus placebo in the 180 mg dose group at week 12 (46%, 95% CI 22 to 69; appendix p 30).

Although there were no statistically significant differences between otilimab dose groups and placebo in mean HAQ-DI scores at weeks 4 and 12, a minimal clinically important difference versus placebo was observed at week 12 in the 180 mg dose group (–0·24, 95% CI –0·49 to 0·01; p=0·059; figure 3B). At week 12, treatment with otilimab was associated with significant improvements in PtGA in all dose groups from 45 mg and above versus placebo; the largest difference versus placebo was observed with the 90 mg dose (–17·40, 95% CI –27·44 to –7·35; p=0·0008) and the difference between 180 mg and placebo was –17·18 (95% CI –27·27 to –7·10; p=0·0009; figure 3C; appendix p 27). A dose-dependent decrease was observed in fatigue (FACIT-Fatigue) from week 4, reaching a statistically significant improvement at week 12 with the 180 mg dose (difference from placebo 5·33, 95% CI 1·77 to 8·89; p=0·0035; figure 3D). There were statistically significant differences over placebo in BFI-Q3 with all doses from 45 mg at week 12. The largest difference from placebo in BFI-Q3 to week 12 was observed in the 180 mg dose group (–1·57, 95% CI –2·53 to –0·62; p=0·0013; appendix pp 10, 29).

There was a dose-dependent improvement in SF-36 scores, observed in all SF-36 domains (general health, bodily pain, mental health, physical functioning, role emotional, role physical, social functioning, and vitality) with all doses of otilimab at week 12 compared with placebo (except for the 22·5 mg, 45 mg, and 90 mg dose groups in the social functioning domain). For the otilimab 180 mg dose the difference versus placebo in SF-36 physical score was 4·11 (95% CI 1·22 to 7·01; p=0·0056) at week 4 and 3·55 (95% CI 0·22 to 6·88; p=0·037) at week 12 (appendix p 28). Consistent with results from VAS assessment of pain, there was a significant improvement in SF-36 bodily pain scores at week 4 (otilimab 180 mg difference *vs* placebo 5·08, 95% CI 2·14 to 8·03; p=0·0008); the improvement over placebo was observed up to week 12 for otilimab 180 mg, when

	Placebo (n=37)	Otilimab				
		22·5 mg (n=37)	45 mg (n=37)	90 mg (n=37)	135 mg (n=37)	180 mg (n=37)
Any adverse events	18 (49%); 27	19 (51%); 36	24 (65%); 59	22 (59%); 54	19 (51%); 48	24 (65%); 64
Adverse events leading to discontinuation of study medication	0	0	0	2 (5%); 2	0	2 (5%); 2
Serious adverse events	0	2 (5%); 2	1 (3%); 1	2 (5%); 3	1 (3%); 1	0
Treatment-related adverse events	2 (5%); 2	9 (24%); 15	6 (16%); 13	6 (16%); 7	5 (14%); 7	9 (24%); 19
Common adverse events*						
Nasopharyngitis	1 (3%); 1	3 (8%); 3	7 (19%); 10	3 (8%); 3	6 (16%); 6	9 (24%); 12
Upper respiratory tract infection	3 (8%); 3	2 (5%); 2	1 (3%); 1	2 (5%); 2	2 (5%); 3	3 (8%); 4
Anaemia	0	2 (5%); 2	1 (3%); 1	0	2 (5%); 3	5 (14%); 5
Alanine aminotransferase increase	0	1 (3%); 1	3 (8%); 6	2 (5%); 2	2 (5%); 2	0

Data are n (%); number of occurrences. *Adverse events occurring in >5% of patients.

Table 2: **Pre-escape adverse events (intention-to-treat population)**

	Placebo (n=33)	Otilimab			
		22·5 mg (n=30)	45 mg (n=27)	90 mg (n=25)	135 mg (n=28)
Any adverse events	22 (67%); 50	16 (53%); 40	11 (41%); 47	10 (40%); 19	17 (61%); 38
Adverse events leading to discontinuation of study medication	1 (3%); 1	1 (3%); 1	0	0	0
Serious adverse events	1 (3%); 1	0	0	0	1 (4%); 1
Treatment-related adverse events	5 (15%); 6	6 (20%); 16	4 (15%); 20	0	6 (21%); 12
Common adverse events*					
Nasopharyngitis	7 (21%); 7	3 (10%); 3	1 (4%); 1	2 (8%); 3	2 (7%); 2
Upper respiratory tract infection	0	3 (10%); 4	2 (7%); 2	0	5 (18%); 6
Anaemia	0	1 (3%); 1	0	0	2 (7%); 2
Alanine aminotransferase increase	2 (6%); 2	0	2 (7%); 2	1 (4%); 1	1 (4%); 2

Data are n (%); number of occurrences. *Adverse events occurring in >5% of patients.

Table 3: **Post-escape adverse events (intention-to-treat population)**

statistical significance was not reached at week 12 (3·43, –0·13 to 6·99; p=0·059). No significant differences were observed in SF-36 mental score at week 4 and at week 12 for all doses. The difference versus placebo for 180 mg dose was 0·10 (95% CI –4·01 to 4·20; p=0·96) at week 4 and 3·25 (95% CI –1·05 to 7·54; p=0·14) at week 12 (appendix p 28).

The mean serum concentration of otilimab increased in a dose-dependent manner and peaked at week 4; the decline in serum concentrations coincided with the transition to every-other-week dosing from week 6 (appendix p 11). In the 180 mg group, observed mean trough concentration was 713–936 ng/mL between week 8 and week 52 (appendix p 12). The otilimab trough concentrations were lower than predicted from historic pharmacokinetic data (GSK unpublished results). Consistent with pharmacokinetic observations, the concentration of GM-CSF–otilimab complex also increased in a dose-dependent manner, peaking at week 4, and then declined after the switch to every other week dosing after week 6 (appendix p 11). Separation between the 135 mg and 180 mg dose and overall decline was observed from week 8, suggesting the target was no longer saturated.

Adverse event rates were balanced across all treatment groups and most adverse events were mild or moderate (tables 2, 3). No dose effect on adverse events or other safety parameters were observed in the otilimab groups. The most common treatment-related adverse events were nasopharyngitis, upper respiratory tract infection, and anaemia pre-escape (table 2), and nasopharyngitis and upper respiratory tract infection post escape (table 3). The rates of cytopenia and serious infections were low and there was no notable incidence of anti-drug antibodies across treatment groups. There were no deaths, malignancies, or venous thromboembolism, nor any events of pulmonary toxicity of clinical concern. Changes in D_{LCO} were infrequent and small; persistent (≥15 days) D_{LCO} decrease from baseline of more than 15% was observed in one patient in each otilimab treatment group (except 90 mg) pre-escape, and in six patients post escape (two patients in each of the groups originally randomised to placebo, 22·5 mg and 135 mg). These changes were not considered to be dose related or clinically significant. One patient had persistent dyspnoea in the otilimab 90 mg group, pre-escape, beginning on day 8; the patient showed no decrease in D_{LCO}, and no substantial change in FEV_1

and forced vital capacity between baseline and week 12. Pulmonary events led to treatment discontinuation in three patients. Mild pulmonary fibrosis was reported in one patient in the otilimab 22·5 mg group, which occurred post escape to the 180 mg dose. One patient in the otilimab 180 mg group had mild persistent D_{LCO} decrease, which was associated with acute bronchitis. Mild persistent dyspnoea was reported in one patient in the placebo group after escape to otilimab 180 mg dose: no decrease in D_{LCO} was observed and a small (<5%) decrease in spirometry assessments was reported; the event was assessed as not related to study medication. None of the pulmonary events were assessed as pulmonary alveolar proteinosis.

Pre-escape, eight patients had nine adverse events of special interest: injection-site reactions, neutropenia, serious infection, persistent dyspnoea, and persistent cough (appendix p 31). There were six post escape adverse events of special interest reported by four patients during the study period: injection-site reactions and persistent dyspnoea (appendix p 31). There were no events of hypersensitivity reactions, opportunistic infections, or pulmonary alveolar proteinosis reported.

Six patients had serious adverse events pre-escape (foot fracture, arthralgia, myocardial infarction, oesophageal spasm, acute pyelonephritis, uterine leiomyoma, and dizziness; none were reported in the otilimab 180 mg or placebo groups; appendix p 32). After escape to the 180 mg group, one event of ankle fracture was reported in the placebo group and one event of rheumatoid arthritis was reported in the 135 mg group. None of the serious adverse events (pre- or post escape) were deemed to be related to study treatment.

Discussion

In this phase 2b dose-ranging study, the primary endpoint at week 24 was not achieved. Patients had severe rheumatoid arthritis at baseline, characterised by higher DAS28-CRP, pain, and HAQ-DI compared with other phase 2b studies targeting GM-CSF.[16] Despite this high baseline disease severity, otilimab in combination with methotrexate showed clinically meaningful efficacy over 12 weeks of treatment with a rapid reduction in DAS28-CRP similar to other approved biologic agents,[20,21] and the treatment was well tolerated.

The primary endpoint of DAS28-CRP remission was chosen on the basis of its importance as a EULAR treatment goal in rheumatoid arthritis. Escape therapy ensured that only patients who obtained a meaningful benefit from their assigned treatment would continue treatment at the assigned dose throughout the study.[22] This approach was based on the rationale that an optimised treat-to-target dosing regimen might result in a larger proportion of patients achieving remission.[22] The clinical benefit of frequent monitoring and treatment adjustments according to a prespecified target has been shown in other randomised trials.[23]

Otilimab serum concentrations were lower than expected based on historic data from healthy volunteers (GSK data on file), resulting in suboptimal exposure during every-other-week dosing, from week 6 onwards. This discrepancy is likely due to the high apparent clearance of otilimab.[24] Consistent with this, concentrations of serum GM-CSF–otilimab complex showed that full target engagement was not achieved from week 6 onwards with every-other-week dosing. The findings confirm and extend those from a phase 2a study,[14] which assessed otilimab 180 mg compared with placebo in patients with rheumatoid arthritis receiving concomitant methotrexate over 12 weeks.

Previous studies[2,3,25] have shown that many patients who achieve low disease activity still report significant pain that negatively affects their quality of life and may produce biological, psychological, and social changes that could affect the future response to painful stimuli. Consequently, pain is prioritised by patients with rheumatoid arthritis as a key unmet need.[2] Despite suboptimal pharmacological exposure with bi-weekly otilimab doses, and our study not reaching statistical significance for its primary endpoint of DAS28-CRP <2·6 remission, there was a rapid, sustained, and consistent improvement in patient-reported outcome endpoints. In particular, the improvement in pain VAS score was significantly greater than placebo at doses 45 mg or more at weeks 8 and 12. Similarly, there were substantial improvements in other patient-reported outcome measures, including function, disability, health-related quality of life, and fatigue. Of note, the 90 mg dose group had fewer patients who escaped to the 180 mg dose. A slight imbalance in disease characteristics was also observed between these groups. Although this finding was investigated, no explanation was found. It could be an artifact of the small sample size or the baseline characteristics, but this is not confirmed.

The pathophysiology of rheumatoid arthritis is complex, and the biological basis of joint pain could in part be different from that of inflammation and bone damage.[2,5,10] Studies[26,27] have shown that discrete subsets of synovial fibroblasts and macrophages that reside in distinct anatomical compartments of the joint are responsible for inflammation, tissue damage, and repair. These observations have provided a cellular basis for the partial dissociation of inflammation and damage in rheumatoid arthritis and osteoarthritis. However, there has not been any formal exploration in a clinical study of the mechanisms by which disease activity, remission, and pain relate to each other in either rheumatoid arthritis or osteoarthritis. Traditional anti-TNF therapies reduce inflammation and halt bone destruction,[28] but might not target all the cell types associated with pain. GM-CSF has a key role in the development of inflammatory and arthritic pain,[5] and inhibition of the GM-CSF→JMJD3 (jumonji domain-containing protein 3)→IRF4 (interferon regulatory factor 4)→CCL17 pathway ameliorates pain in osteoarthritis.[10] In our study, although the improvement in pain was accompanied by decreased inflammation, as evidenced

by reduced CRP (and swollen joint count) at week 12, our findings suggest that the therapeutic response with otilimab is predominantly driven by improvements in clinical parameters, reflected by the large CDAI responses not affected by CRP changes. The beneficial effect of otilimab on pain continued to progress beyond CRP reduction. These findings raise the possibility that the effects of treatment on pain and inflammation might be partly dissociated in rheumatoid arthritis; further studies are required to explore this more fully.

One limitation of our study was that its design resulted in a high percentage of escape from the placebo and the lower otilimab dose groups after week 12. As such, the nonsignificant difference versus placebo in DAS28-CRP at week 24 should be interpreted with consideration of a large proportion of patients in the placebo group having received otilimab 180 mg. The high percentage of escape, together with lower than expected exposure of otilimab, is likely to have contributed to the relatively low patient numbers and remission rates at the primary endpoint, week 24. Despite this finding, the observed improvements in disease activity and the rapid reduction of associated pain over 12 weeks reflects important clinical benefits, especially for patients with long-standing active disease.[2] Phase 3 studies are underway to further establish the efficacy of otilimab in a larger population and over a longer period, using an optimised dose and regimen (NCT03980483, NCT03970837, NCT04134728).[24]

The study design allowed the safety of otilimab to be assessed over 50 weeks of treatment and 12 weeks of subsequent follow-up. No clinically significant unexpected safety findings were observed. Otilimab was well tolerated, with low rates of cytopenia and serious infections, no clinically significant incidence of anti-drug antibodies, no deaths and no pulmonary toxicity events of clinical concern (including pulmonary alveolar proteinosis), consistent with previous studies of otilimab and other antibodies targeting GM-CSF signalling.[13,14,16]

In conclusion, despite the suboptimal exposure with bi-weekly dosing from week 6, patients receiving otilimab showed significant reductions in rheumatoid arthritis disease activity at week 12, particularly on joint swelling and tenderness and patient-reported outcomes involving pain. The results of this study support further clinical development, given the observed benefit:risk ratio of inhibiting GM-CSF with otilimab in the treatment of active rheumatoid arthritis. Furthermore, they suggest that targeting GM-CSF might not only reduce disease activity but also markedly improve pain and function.

Contributors

CDB, KD, ML, NM, JP, RW, and PPT contributed to the conception and design of the study. CDB, JAS-C, and VZ contributed to the acquisition of data. CDB, BB, KD, EF, AG, CH, DI, ML, JP, DS, RW, and PPT contributed to data analysis or interpretation. All authors were involved in development of the manuscript and approved the final version.

Declaration of interests

CDB has received payments from GSK for consultancy work related to GM-CSF biology. BB, KD, AG, CH, DI, ML, JP, and DS are employees and stockholders in GSK. EF, NM, RW, and PPT were employees and stockholders of GSK at the time of study conduct. JAS-C and VZ declare no competing interests.

Data sharing

Anonymised individual participant data and study documents can be requested for further research from the Clinical Study Data Request website.

For **Clinical Study Data Request** see www.clinicalstudydata request.com

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