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## CLINICAL SCIENCE

# Anti-GM-CSF otilimab versus sarilumab or placebo in patients with rheumatoid arthritis and inadequate response to targeted therapies: a phase III randomised trial (contRAst 3)

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Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/ard-2023-224449>).

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Received 18 May 2023

Accepted 23 August 2023

Published Online First

11 September 2023

## ABSTRACT

**Objectives** To investigate the efficacy and safety of otilimab, an anti-granulocyte-macrophage colony-stimulating factor antibody, in patients with active rheumatoid arthritis and an inadequate response to conventional synthetic (cs) and biologic disease-modifying antirheumatic drugs (DMARDs) and/or Janus kinase inhibitors.

**Methods** ContRAst 3 was a 24-week, phase III, multicentre, randomised controlled trial. Patients received subcutaneous otilimab (90/150 mg once weekly), subcutaneous sarilumab (200 mg every 2 weeks) or placebo for 12 weeks, in addition to csDMARDs. Patients receiving placebo were switched to active interventions at week 12 and treatment continued to week 24. The primary end point was the proportion of patients achieving an American College of Rheumatology  $\geq 20\%$  response (ACR20) at week 12.

**Results** Overall, 549 patients received treatment. At week 12, there was no significant difference in the proportion of ACR20 responders with otilimab 90 mg and 150 mg versus placebo (45% ( $p=0.2868$ ) and 51% ( $p=0.0596$ ) vs 38%, respectively). There were no significant differences in Clinical Disease Activity Index, Health Assessment Questionnaire-Disability Index, pain Visual Analogue Scale or Functional Assessment of Chronic Illness Therapy-Fatigue scores with otilimab versus placebo at week 12. Sarilumab demonstrated superiority to otilimab in ACR20 response and secondary end points. The incidence of adverse or serious adverse events was similar across treatment groups.

**Conclusions** Otilimab demonstrated an acceptable safety profile but failed to achieve the primary end point of ACR20 and improve secondary end points versus placebo or demonstrate non-inferiority to sarilumab in this patient population.

**Trial registration number** NCT04134728.

## INTRODUCTION

Despite the range of disease-modifying anti-rheumatic drugs (DMARDs) that have transformed the therapeutic landscape of rheumatoid arthritis (RA), there are patients who fail to achieve

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Despite recent advances in rheumatoid arthritis (RA) therapy, there are patients who are refractory and remain symptomatic despite having been treated with all currently available treatment options.
- ⇒ It has been reported multiple times that response to therapy decreases, with subsequent lines of therapy; therefore, patients with multiple advanced therapeutic failures represent a current unmet need in RA treatment.
- ⇒ The granulocyte-macrophage colony-stimulating factor antibody (GM-CSF) pathway has been identified as a promising target for the treatment of RA and has been postulated to play a role in pain responses.
- ⇒ While preclinical studies have demonstrated that GM-CSF inhibition improved inflammatory arthritis and pain, clinical efficacy trials of monoclonal antibodies targeting GM-CSF or the GM-CSF receptor in patients with RA has generated mixed results.

remission or low disease activity (LDA) with these treatment options.<sup>1,2</sup> It has been reported that the response to RA therapy generally decreases with each subsequent line of biologic (b) DMARD.<sup>3</sup> A 2018 observational study of over 13 000 patients with RA in Britain has estimated that 6% of patients are refractory to multiple bDMARDs<sup>4</sup>; therefore, many patients continue to have a substantial symptom burden despite treatment.<sup>5</sup> The approval of Janus kinase inhibitors (JAKis) has provided a novel, alternative mechanism of action (MoA) for patients with an inadequate response (IR) to bDMARDs; however, there are patients who also fail to respond to this MoA as well.<sup>6</sup> Patients are generally considered 'difficult-to-treat' if they have failed  $\geq 2$  bDMARDs/targeted synthetic (ts) DMARDs of different MoAs, after failing conventional synthetic (cs) DMARD therapy (unless contra-indicated).<sup>7</sup> Furthermore, a number of patients who



► <https://dx.doi.org/10.1136/ard-2023-2244904>



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**To cite:** Taylor PC, Weinblatt ME, McInnes IB, et al. *Ann Rheum Dis* 2023;**82**:1527–1537.

# WHAT THIS STUDY ADDS

- ⇒ This phase III randomised controlled trial investigated the safety and efficacy of otilimab, a high-affinity anti-GM-CSF monoclonal antibody, in patients with a previous inadequate response to conventional synthetic and biologic disease-modifying antirheumatic drugs and/or Janus kinase inhibitors.
- ⇒ Otilimab failed to demonstrate a difference in American College of Rheumatology  $\geq 20\%$  response compared with placebo, did not improve secondary end points and failed to demonstrate non-inferiority to sarilumab in this RA population.
- ⇒ This trial corroborates previous sarilumab studies and provides robust clinical efficacy, safety and pharmacokinetic/pharmacodynamic data for an anti-GM-CSF monoclonal antibody in a geographically diverse population of patients with RA who have had multiple therapeutic failures.

# HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ For many years, GM-CSF has been considered an attractive target in the treatment of RA, and a novel mechanism of action might have the potential to be effective in patients who fail to respond to currently approved therapies.
- ⇒ Although previous phase I and phase II randomised controlled trials (RCTs) have reported the benefit of targeting the GM-CSF pathway, to date, only otilimab has progressed to phase III.
- ⇒ While negative, results from this RCT may help to inform clinical trial design and therapeutic target selection in future approaches to novel pharmacotherapy in this RA patient population.

have achieved a good clinical response may continue to experience RA symptoms such as pain and fatigue.<sup>8–10</sup> Therefore, despite recent significant advances in RA therapy, there remains an unmet need for novel treatments in the management of RA.<sup>7</sup>

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been implicated in a number of pathogenic processes in RA such as promoting the differentiation of inflammatory monocytes, macrophages and dendritic cells, and enhancing the production of tumour necrosis factor (TNF), interleukin (IL)-1 and IL-6—pro-inflammatory cytokines that are a hallmark of RA.<sup>11–13</sup> Preclinical studies have shown GM-CSF-targeting strategies to be efficacious in impairing disease development or reducing disease activity in collagen-induced murine models of inflammatory arthritis.<sup>13 14</sup> Studies have also indicated that GM-CSF is a mediator of inflammatory pain and arthritic pain, and that it plays a role in sensitising neurons most likely via neuroimmune interactions with sensory neurons.<sup>15–17</sup> Given the plausible potential roles of GM-CSF in both RA disease development and pain mechanisms, the GM-CSF pathway was an attractive target in the development of new therapeutics.<sup>13 15 16 18–20</sup>

Otilimab is a high-affinity anti-GM-CSF monoclonal antibody that,<sup>21</sup> when used in combination with methotrexate (MTX), demonstrated clinically meaningful improvements in disease activity and pain in a phase IIb dose-ranging trial in RA.<sup>22</sup> This phase III randomised controlled trial (RCT) evaluated the efficacy and safety of otilimab versus placebo or sarilumab, a monoclonal antibody against the IL-6 receptor (IL-6R), in combination with csDMARDs, in adult patients with active RA and a prior IR to csDMARDs and bDMARDs and/or JAKis.

# METHODS

## Trial design

ContrASt 3 was a 24-week, phase III, multicentre, double-blind, RCT (study number 202018; NCT04134728), conducted at 131 sites across 15 countries (online supplemental table 1) from 31 October 2019 to 1 February 2022, coinciding with the COVID-19 pandemic. Patients were randomised 6:6:6:1:1:1 to receive otilimab 90 mg subcutaneously weekly, otilimab 150 mg subcutaneously weekly, sarilumab 200 mg subcutaneously every 2 weeks or placebo, with background csDMARDs. Otilimab doses were selected based on pharmacokinetic (PK), efficacy, safety and exposure-response and dose-response modelling of data from the phase IIb trial, BAROQUE.<sup>22</sup> The weekly regimen was selected to overcome the apparent high clearance rate observed in BAROQUE.<sup>22</sup> Patients initially treated with otilimab or sarilumab continued treatment for 24 weeks. Patients allocated to placebo were treated to week 12 (time of primary end point; period 1), after which they were switched to their respective active interventions and continued treatment from week 12 to week 24 (period 2). At week 24, patients had the option to transition into the long-term extension trial (contrASt X; NCT04333147). Patients who did not transition into contrASt X were seen for a safety follow-up visit at week 34 (figure 1).

An amendment to the protocol was made after trial commencement whereby the exclusion criterion of the history or presence of myocardial infarction was reduced from within 12 months, to within 3 months, as 3 months was deemed an appropriate period of time to stabilise ischaemic heart disease.

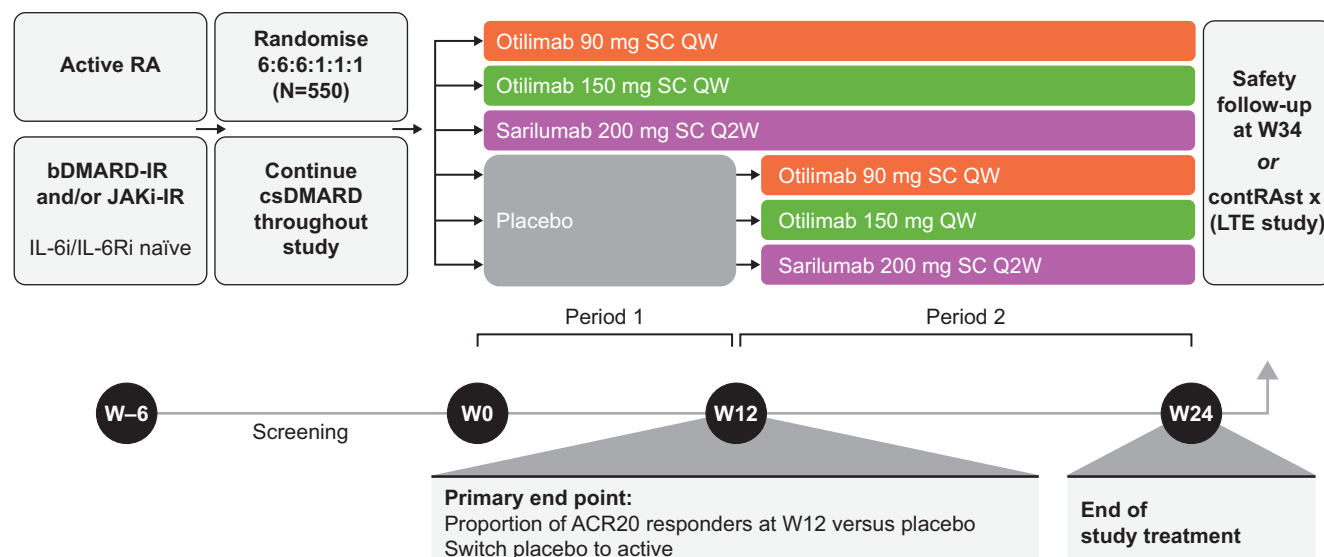
## Patients

Eligible patients were adults (aged  $\geq 18$  years) with a clinical diagnosis of RA, per American College of Rheumatology (ACR)/EULAR 2010 Classification Criteria,<sup>23</sup> a global functional status in RA of class I, II or III per the ACR 1991 revised criteria,<sup>24</sup> a disease duration  $\geq 6$  months at screening, active disease at screening and baseline, defined by tender joint count (TJC)  $\geq 6/68$  and swollen joint count (SJC)  $\geq 6/66$  and a high-sensitivity C reactive protein measurement  $\geq 3$  mg/L. Patients were required to have had an IR despite current treatment with a stable dose of 1 or 2 of the permitted csDMARDs (online supplemental table 2) for  $\geq 12$  weeks prior to day 1. Patients must also have had an IR to an approved dose of  $\geq 1$  bDMARD (excluding anti-GM-CSF/GM-CSF receptor (R) and anti-IL-6/IL-6R therapies) and/or  $\geq 1$  JAKi with or without concomitant csDMARDs. There was no limit to the number of prior b/tsDMARDs received. Any current bDMARDs and JAKis were required to be discontinued for a defined time period prior to randomisation that was dependent on the specific treatment (online supplemental table 3).

Patients were excluded if they had active or recurrent infections (patients diagnosed with latent tuberculosis (TB) at screening were treated with isoniazid for  $\geq 4$  weeks prior to randomisation and completed the anti-TB treatment per WHO or national guidelines during the trial), persistent cough or persistent dyspnoea, hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency or a clinically significant abnormal chest radiograph within 12 weeks of screening. The full inclusion/exclusion criteria are provided in the online supplemental materials.

## Randomisation and blinding

Patients were centrally randomised in a blinded manner using an interactive response technology system. Randomisation was stratified by previously failed medication: 1 bDMARD,  $>1$



**Figure 1** Trial design. ACR, American College of Rheumatology; b/cDMARD, biologic/conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin-6; IL-6Ri, IL-6 receptor inhibitor; IR, inadequate response; JAKi, Janus kinase inhibitor; LTE, long-term extension; Q2W, once every 2 weeks; QW, once weekly; RA, rheumatoid arthritis; SC, subcutaneous; W, week.

bDMARD or  $\geq 1$  JAKi (irrespective of prior bDMARD failure). Trial interventions were dispensed by an unblinded pharmacist who ensured that patients and trial investigators remained blinded to the intervention for the entire duration of the study.

### Trial treatments

Patients received subcutaneous injection of otilimab 90 mg or 150 mg once weekly; subcutaneous injection of sarilumab 200 mg every 2 weeks plus subcutaneous injection of placebo (on the alternate weeks to maintain blinding); or subcutaneous injection of placebo weekly, in combination with stable doses of background csDMARDs. Stable oral corticosteroid treatment with a dose  $\leq 10$  mg/day prednisolone or equivalent was permitted throughout the trial. Analgesics, including acetaminophen (paracetamol)  $\leq 4$  g/day were also permitted as rescue medication for pain management, but could not be taken within the 24 hours prior to baseline (day 1) or subsequent assessment visits (online supplemental table 2). Other concomitant csDMARDs, bDMARDs and tsDMARDs were not permitted (online supplemental table 3).

### End points and assessments

The primary end point was the proportion of patients achieving a  $\geq 20\%$  improvement in the ACR criteria (ACR20 response)<sup>25</sup> at week 12 for otilimab 90 mg and 150 mg versus placebo. Major secondary, multiplicity controlled, efficacy end points were change from baseline (CFB) in Health Assessment Questionnaire-Disability Index (HAQ-DI) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue versus placebo at week 12, and CFB in Clinical Disease Activity Index (CDAI), pain Visual Analogue Scale (VAS) score and FACIT-Fatigue at week 24 versus sarilumab (superiority). Additional secondary end points included the proportion of patients achieving CDAI LDA ( $\leq 10$ ) and remission ( $\leq 2.8$ ), ACR20/50/70 response, Disease Activity Score (DAS)28-CRP  $\leq 3.2$  or  $< 2.6$  vs placebo and versus sarilumab at week 12 or versus sarilumab at week 24 as well as CFB in CDAI, DAS28-CRP, HAQ-DI, pain VAS score, ACR components and Short-Form (SF)-36 Physical and Mental Component Summary (PCS and MCS) scores versus placebo or sarilumab at week 12 and versus sarilumab at week 24. Safety

end points included the incidence of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) and CFB in key laboratory parameters at weeks 12 and 24.

### PK/Pharmacodynamic and biomarker assessments

Blood samples for measurement of serum concentrations of otilimab, GM-CSF-otilimab complex and CC motif chemokine ligand (CCL17) were collected on days 1, 8, 15, 29, 85 and 169 for pharmacodynamic (PD) and biomarker assessments, and on days 15, 29, 57, 85, 113 and 169 for PK assessments (post-day 85 data not reported).

### Statistical analysis

A sample size of 525 provided 96% power to detect a 25% difference between otilimab and placebo in ACR20 response rate at week 12 based on a two-sided significance level of 0.05, using a pooled z-test. The primary end point was analysed using logistic regression, comparing otilimab with placebo at week 12, including fixed effects for treatment arm, baseline SJC66 and TJC68 and previously failed medication. To control for multiplicity, the primary and key secondary end points were assessed sequentially in a prespecified hierarchical order (online supplemental figure 1), where otilimab 150 mg was tested before the 90 mg dose. If patients agreed to continue to participate in the trial, their data continued to be collected and were used in the analysis. Missing data for this primary estimand were handled using multiple imputation (online supplemental materials). Supplementary analysis using non-responder imputation, where patients who discontinued treatment were considered non-responders, was conducted.

Binary end points were analysed using logistic regression and continuous end points using analysis of covariance. The efficacy population was the intent-to-treat (ITT) population defined as all patients who were randomised and received  $\geq 1$  dose of trial intervention. The safety population included all randomised patients who received  $\geq 1$  dose of trial treatment. The PK population included all patients in the safety population who had  $\geq 1$  non-missing PK assessment.

### Patient and public involvement

Patients were involved in patient advisory boards and in-person touchpoints in which the trial design and end points were

discussed. There was no further patient or public involvement in the conduct or reporting of the trial.

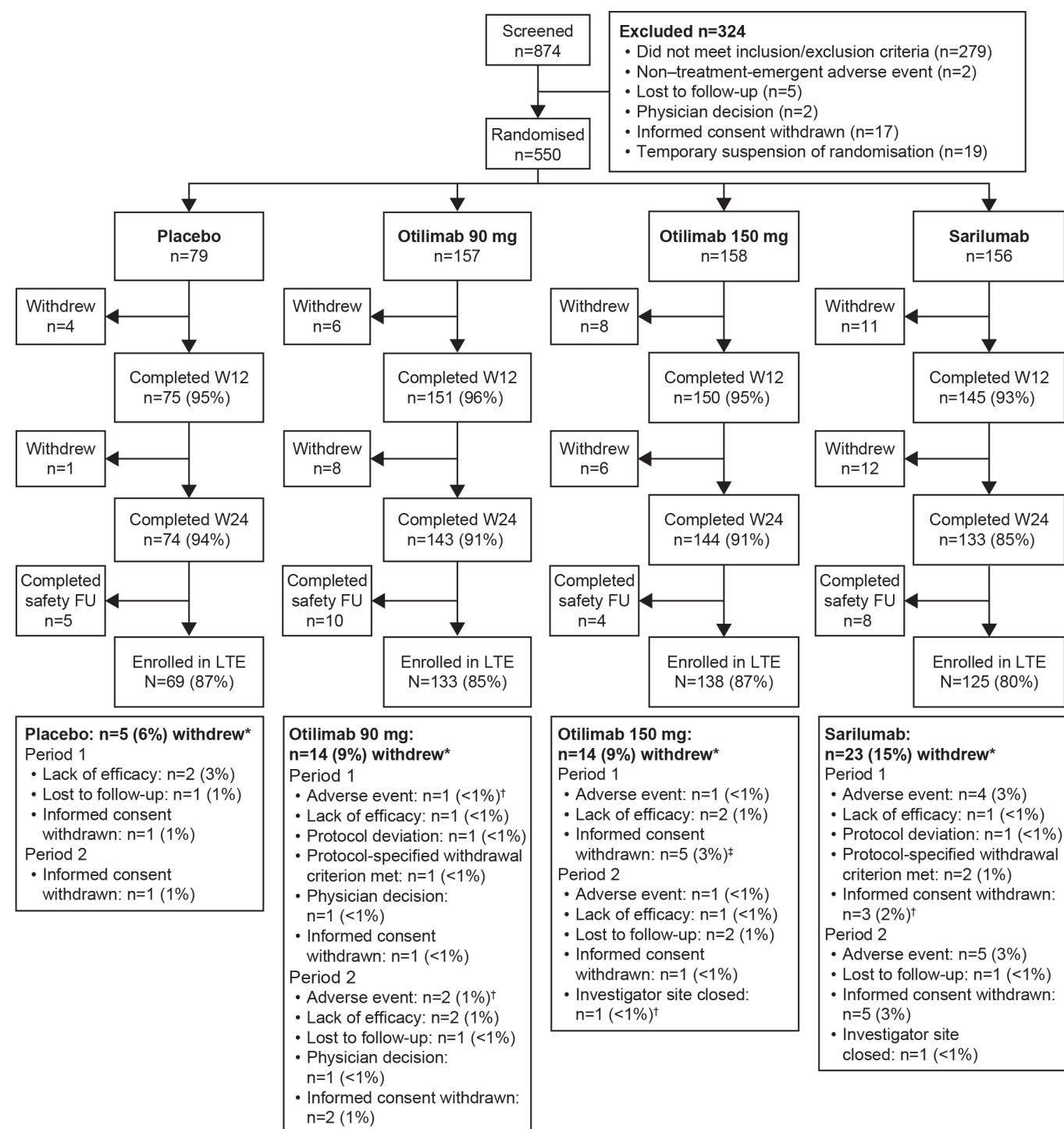
## RESULTS

### Trial population

Of the 874 patients who were screened, 550 met the inclusion criteria and were randomised; 1 patient did not receive a dose of trial treatment, therefore, 549 patients were included in the

ITT and safety populations, 27 patients completed the safety follow-up at week 34, while 465 entered contrAST X (figure 2).

Baseline demographics and clinical characteristics were generally balanced across treatment groups (table 1). Per the trial design, patients were permitted to continue receiving background csDMARDs (not provided as part of the trial); 83%–89% of patients were receiving MTX at baseline, while 8%–11% were receiving more than one csDMARD. In this



**Figure 2** Patient disposition. \*Only one primary reason for treatment discontinuation permitted. †Due to COVID-19 pandemic (n=1). ‡Only one patient in otilimab 90 mg and 150 mg groups and two patients in sarilumab group discontinued treatment due to COVID-19 pandemic. One patient randomised to otilimab 90 mg did not receive any dose of the trial medication. Period 1 is defined as time from randomisation to week 12, period 2 is defined as time from first dose post-week 12 until date of trial completion/withdrawal/treatment withdrawal plus follow-up, whichever is earlier. FU, follow-up; LTE, long-term extension; W, week.



**Table 1** Demographics and baseline characteristics

	Pooled placebo (n=79)	Otilimab 90 mg once weekly (n=156)	Otilimab 150 mg once weekly (n=158)	Sarilumab 200 mg once every 2 weeks (n=156)	Total (n=549)
<b>Demographics</b>					
Female, n (%)	65 (82)	134 (86)	135 (85)	132 (85)	466 (85)
Age, years, * mean (SD)	55.5 (10.64)	56.7 (10.59)	56.0 (10.52)	57.5 (10.69)	56.6 (10.60)
Asian	7 (9)	13 (8)	15 (9)	12 (8)	47 (9)
Black or African-American	4 (5)	5 (3)	8 (5)	6 (4)	23 (4)
White	67 (85)	137 (88)	133 (84)	138 (88)	475 (87)
<b>Baseline clinical characteristics</b>					
TJC 68, mean (SD)	22.14 (14.39)	22.55 (13.11)	23.63 (13.78)	24.08 (13.55)	23.24 (13.60)
SJC 66, mean (SD)	13.74 (7.55)	14.63 (8.51)	14.95 (9.05)	15.59 (9.38)	14.87 (8.79)
Pain VAS score, mean (SD)	67.04 (22.85)	67.38 (23.17)	67.06 (20.50)	65.39 (21.72)	66.67 (21.91)
PtGA, mean (SD)	62.72 (21.80)	64.67 (20.81)	65.93 (19.61)	64.67 (21.23)	64.75 (20.70)
PhGA, mean (SD)	63.65 (19.31)	64.05 (16.52)	68.83 (17.25)	68.86 (17.65)	66.75 (17.59)
CRP (mg/L), mean (SD)	19.65 (22.75)	16.94 (21.74)	16.51 (17.531)	19.89 (34.54)	18.04 (25.18)
CDAI, mean (SD)	36.06 (11.63)	38.09 (11.90)	39.42 (11.48)	39.55 (12.37)	38.60 (11.91)
DAS28-CRP, mean (SD)	5.60 (0.90)	5.69 (0.86)	5.81 (0.81)	5.76 (0.91)	5.73 (0.87)
HAQ-DI, mean (SD)	1.55 (0.68)	1.65 (0.62)	1.66 (0.65)	1.64 (0.68)	1.64 (0.65)
SF-36 MCS, mean (SD)	45.18 (13.30)	45.85 (11.22)	45.95 (11.22)	46.45 (10.30)	45.96 (11.27)
SF-36 PCS, mean (SD)	33.45 (7.75)	32.23 (7.72)	32.14 (7.81)	32.87 (7.80)	32.56 (7.76)
FACIT-Fatigue, mean (SD)	26.48 (13.04)	26.36 (11.19)	26.56 (11.18)	27.40 (11.32)	26.73 (11.49)
<b>RA disease history</b>					
Time since RA diagnosis (years), mean (SD)	11.35 (7.72)	12.24 (8.48)	10.73 (7.26)	13.17 (9.27)	11.94 (8.32)
Stratum (previously failed medication), n (%)					
1 bDMARD	39 (49)	78 (50)	79 (50)	77 (49)	273 (50)
>1 bDMARD	14 (18)	27 (17)	29 (18)	31 (20)	101 (18)
≥1 JAKi	26 (33)	51 (33)	50 (32)	48 (31)	175 (32)
<b>RA medications taken at baseline (day 1)</b>					
MTX, n (%)	68 (86)	139 (89)	131 (83)	134 (86)	472 (86)
MTX dose (mg/week), mean (SD)	17.00 (4.92)	17.36 (4.81)	17.19 (4.60)	16.88 (4.52)	17.12 (4.68)
csDMARDs >1, n (%)†	9 (11)	16 (10)	16 (10)	13 (8)	54 (10)
Corticosteroids, n (%)‡	40 (51)	70 (45)	75 (47)	73 (47)	258 (47)
Corticosteroid dose (mg/day)‡, mean (SD)	6.94 (7.39)	5.80 (2.51)	5.82 (2.36)	5.78 (2.33)	5.98 (3.64)

\*Age is imputed when full date of birth is not provided.

†csDMARDs other than MTX taken at baseline included hydroxychloroquine, leflunomide, sulfasalazine, leflunomide, iguratimod, bucillamine and tacrolimus.

‡Only includes patients who have taken oral corticosteroids for ≥4 weeks prior to baseline.

bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, Disease Activity Score-28 joints; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; JAKi, Janus kinase inhibitor; MCS, Mental Component Summary; MTX, methotrexate; PCS, Physical Component Summary; PhGA, Physician Global Assessment; PtGA, Patient Global Assessment; RA, rheumatoid arthritis; SD, standard definition; SF-36, Short Form-36 questions; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.

treatment-refractory patient population, 50% of patients had failed one previous bDMARD, 18% had failed >1 bDMARD, 32% had failed ≥1 JAKi (of which approximately half had failed 1 JAK only and the remainder had failed >1bDMARD/JAKi) and 45%–51% were receiving concomitant corticosteroids. The most common prior bDMARDs (used in ≥20% of patients) were etanercept (35%), adalimumab (31%) and the most common tsDMARD was tofacitinib (23%).

### Primary end point

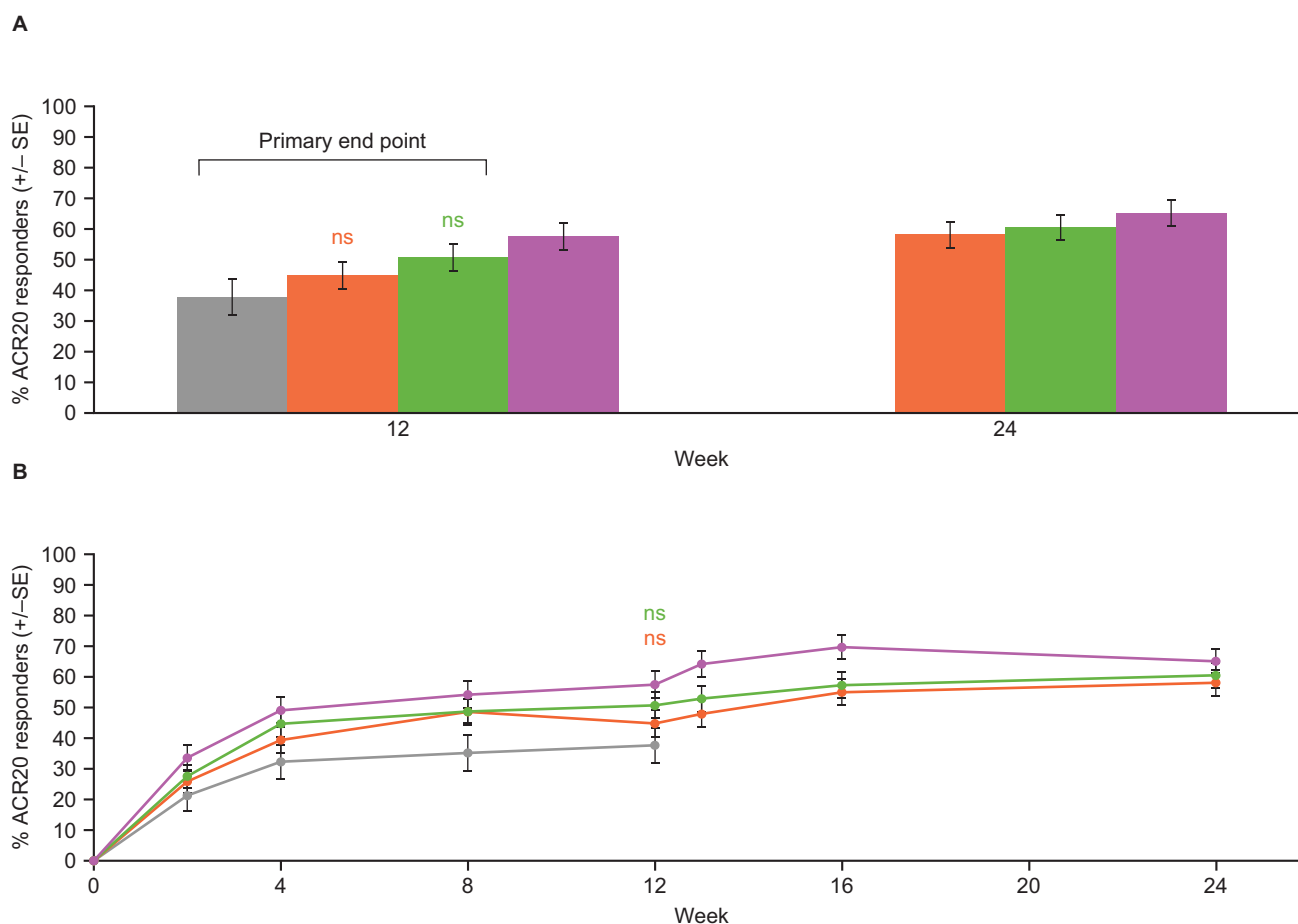
At week 12, while numerically more patients were ACR20 responders with otilimab 90 mg (45%) and 150 mg (51%) vs placebo (38%), this was not statistically significant for either dose ( $p=0.2868$  and  $p=0.0596$ ) and therefore the trial did not meet the primary end point (figure 3, table 2). As a result, irrespective of any  $p$  values obtained, statistical significance cannot be claimed for any of the subsequent end points. Sarilumab treatment resulted in a greater proportion of patients achieving ACR20 response versus placebo ( $p=0.0049$ ).

### Secondary end points

No differences were reported with either dose of otilimab versus placebo in CDAI, HAQ-DI, FACIT-Fatigue and pain VAS score at weeks 12 or 24 (table 2, figure 4, online supplemental table 4), except for otilimab 150 mg which resulted in a numerical reduction in baseline HAQ-DI at week 12 (difference vs placebo:  $-0.17$ ; 95% CI  $-0.32$  to  $-0.03$ ). Sarilumab-treated patients reported meaningful differences versus placebo in HAQ-DI ( $-0.22$ , 95% CI  $-0.37$  to  $-0.08$ ), CDAI ( $-5.35$ , 95% CI  $-8.76$  to  $-1.94$ ) and pain VAS ( $-9.20$ , 95% CI  $-16.19$  to  $-2.21$ ) at week 12 (table 2, figure 4, online supplemental figure 2).

Supplementary analysis of ACR20 response using non-responder imputation showed similar results to the primary analysis (online supplemental figure 3), and similar proportions of ACR20 responders were observed in the subgroup analyses of region and prior failed DMARDs (online supplemental figure 4). No meaningful differences were reported in DAS28-CRP, DAS28-CRP ≤3.2, DAS28-CRP <2.6, CDAI remission, ACR50/70 response, SF-36 PCS or SF-36 MCS

■ Pooled PBO (N=79) ■ Otilimab 90 mg QW (N=156) ■ Otilimab 150 mg QW (N=158) ■ Sarilumab 200 mg Q2W (N=156)



**Figure 3** Proportion of patients achieving ACR20 at (A) weeks 12 and 24 and (B) each assessment visit. Statistical comparison of otilimab versus placebo. P values for all other comparisons are provided in the data tables. ACR, American College of Rheumatology; ns, not significant; PBO, placebo; Q2W, once every 2 weeks; QW, once weekly; SE, standard error.

with either dose of otilimab versus placebo (online supplemental figures 5–7 and online supplemental tables 5 and 6). In contrast, at week 12, sarilumab treatment resulted in a meaningful difference versus placebo in DAS28-CRP reduction ( $-1.07$ , 95% CI  $-1.41$  to  $-0.74$ ) and increases in the proportion of patients achieving DAS28-CRP  $\leq 3.2$  (OR vs placebo: 5.58, 95% CI 2.48 to 12.56), DAS28-CRP  $< 2.6$  (OR vs placebo: 22.01, 95% CI 2.89 to 167.75) and CDAI  $\leq 10$  (3.03, 95% CI 1.37 to 6.67). As expected with the MoA of sarilumab, a substantial reduction from baseline CRP was observed, compared with both placebo and otilimab, while only marginal differences in CRP and Physician Global Assessment were reported with otilimab 90 mg and 150 mg, respectively, and no meaningful differences in any of the remaining ACR core measures (online supplemental tables 5 and 6).

### Safety

The incidence of AEs up to week 12 was similar between placebo (n=37, 47%), otilimab 90 mg (n=65, 42%), otilimab 150 mg (n=63, 40%) and sarilumab (n=72, 46%). The incidence of AEs remained similar across all active treatments up to week 24 (otilimab 90 mg: n=95, 59%; otilimab 150 mg: n=99, 63%; sarilumab: n=96, 63%; table 3). A safety summary following the week 12 switch from placebo to active treatment is provided in online supplemental table 7. The most common AEs ( $\geq 5\%$ )

were injection-site reactions, RA and neutropenia up to week 12 and injection-site reactions, urinary tract infection, increased alanine transaminase (ALT), COVID-19, neutropenia and cough up to week 24 (online supplemental table 8).

The incidence of any SAE up to week 12 was  $\leq 3\%$  across all treatment groups. By week 24, the incidence of SAEs was 5% (n=8) for otilimab 90 mg,  $< 1\%$  (n=1) for otilimab 150 mg and 8% (n=12) for sarilumab (table 3). The incidence of each individual SAE was  $\leq 1\%$  in any treatment group (online supplemental table 9).

The incidence of AESIs up to week 12 was 0% (n=0) for placebo, 7% (n=11) for otilimab 90 mg, 4% (n=7) for otilimab 150 mg and 15% (n=24) for sarilumab (online supplemental table 10). By week 24, the incidence of AESI was similar between otilimab 90 mg (n=16; 10%) and otilimab 150 mg (n=15; 9%) and higher in the sarilumab group (n=33; 21%; table 3). Latent TB infection had been detected in four patients (3%) in the otilimab 150 mg group, and in two patients (1%) in the sarilumab group by week 24; following diagnosis by a consultant, these patients received anti-TB therapy per local guidelines. No events of active TB or TB reactivation were reported (online supplemental table 10).

Additionally, no events of PAP, major adverse cardiovascular event (MACE), venous thromboembolism (VTE) or pulmonary embolism (PE) were reported with otilimab or sarilumab in the trial (table 3).

**Table 2** Primary and major secondary end points at week 12

	Pooled placebo (n=79)	Otilimab 90 mg once weekly (n=156)	Otilimab 150 mg once weekly (n=158)	Sarilumab 200 mg once every 2 weeks (n=156)
<b>ACR20</b>				
Responders, % (SE)	37.7 (5.74)	44.8 (4.19)	50.7 (4.12)	57.5 (4.19)
Otilimab versus placebo, OR (95% CI)		1.38 (0.76 to 2.48)	1.75 (0.98 to 3.15)	2.34 (1.29 to 4.23)
P value		0.2868	0.0596	0.0049*
<b>HAQ-DI</b>				
LS mean change (SE)	-0.23 (0.061)	-0.33 (0.044)	-0.41 (0.043)	-0.46 (0.044)
LS mean difference from placebo (95% CI)		-0.10 (-0.24 to 0.05)	-0.17 (-0.32 to -0.03)	-0.22 (-0.37 to -0.08)
P value		0.1982	0.0185†	0.0024*
<b>CDAI</b>				
LS mean change (SE)	-14.86 (1.438)	-16.87 (1.030)	-17.23 (1.018)	-20.22 (1.027)
LS mean difference from placebo (95% CI)		-2.01 (-5.42 to 1.39)	-2.36 (-5.75 to 1.02)	-5.35 (-8.76 to -1.94)
P value		0.2472	0.1715	0.0021*
<b>FACIT-Fatigue</b>				
LS mean change (SE)	5.45 (1.023)	5.50 (0.735)	6.80 (0.724)	7.30 (0.749)
LS mean difference from placebo (95% CI)		0.05 (-2.36 to 2.45)	1.35 (-1.04 to 3.74)	1.85 (-0.56 to 4.26)
P value		0.9693	0.2670	0.1330
<b>Pain VAS score</b>				
LS mean change (SE)	-16.73 (2.939)	-19.35 (2.127)	-21.17 (2.088)	-25.93 (2.120)
LS mean difference from placebo (95% CI)		-2.62 (-9.61 to 4.36)	-4.44 (-11.39 to 2.50)	-9.20 (-16.19 to -2.21)
P value		0.4612	0.2094	0.0099*

\*Statistical significance was not assessed within the step-down multiple testing procedure.

†Not statistically significant within the step-down multiple testing procedure.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; VAS, Visual Analogue Scale.

Two deaths were reported, one in the otilimab 90 mg group, due to COVID-19 pneumonia and one in the sarilumab group, due to drowning; neither were considered related to treatment. There were no clinically meaningful differences with otilimab versus placebo in laboratory parameters; however, the incidence rates of neutropenia and ALT elevation were higher in the sarilumab group than the otilimab group (online supplemental table 11).

### PK/PD and biomarkers

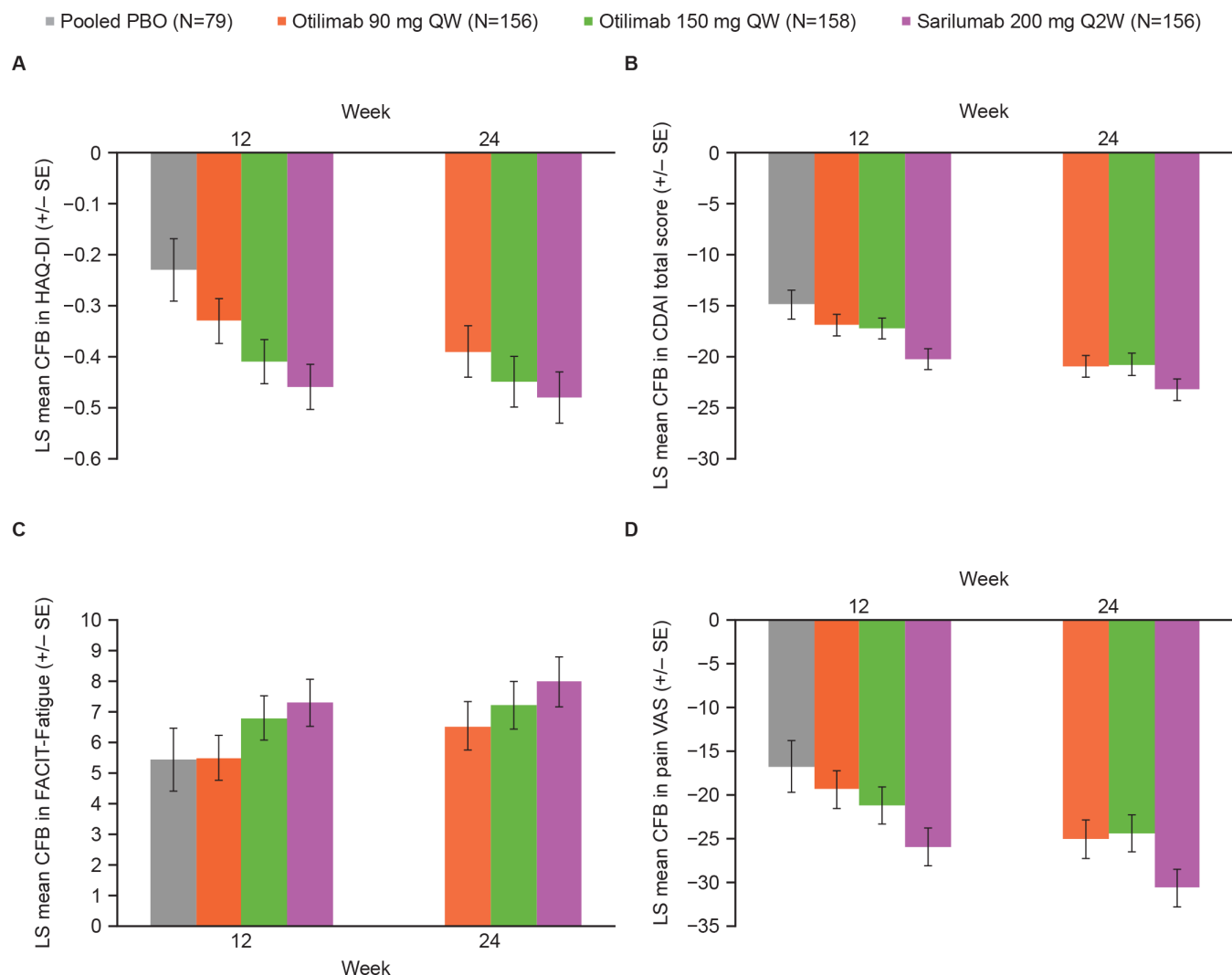
A mean steady state serum otilimab concentration of ~2000 ng/mL (otilimab 90 mg) and ~3150 ng/mL (otilimab 150 mg) was reached between weeks 4 and 8 (online supplemental figure 8). Baseline serum free GM-CSF levels were low (~0.3 µg/L) and similar across treatment groups. Following otilimab treatment, GM-CSF-otilimab complex accumulation showed target engagement which peaked by week 8 (mean 173 ng/L and 226 ng/L for otilimab 90 mg and 150 mg, respectively) and was maintained until week 24. There was some overlap between the two otilimab doses (online supplemental figure 9). Patients treated with either dose of otilimab had a decrease of ~30%–40% in serum concentrations of CCL17 that was not observed with placebo treatment. Serum CCL17 increased initially at week 1 in patients treated with sarilumab before returning to baseline by week 2. Otilimab treatment also resulted in early reductions in IL-6 and matrix metalloprotease-degraded type I collagen (C1M), which were maintained until week 12 (online supplemental figure 10).

### DISCUSSION

The contrASt 3 phase III trial compared otilimab with placebo and the anti-IL-6R monoclonal antibody, sarilumab,

in a broad range of patients with moderate-to-severe RA, including difficult-to-treat and JAKi-IR patients. The trial was conducted in 15 countries across North and South America, Europe, Asia and South Africa, with the COVID-19 pandemic spanning the majority of the trial duration. The primary end point of ACR20 vs placebo at week 12 was not reached with either otilimab dose. Similar outcomes were reported with both otilimab doses, which generally failed to show meaningful improvements versus placebo for any of the secondary end points. While the percentage of ACR20 responders with either otilimab dose at week 12 was in the same range as that reported in the phase II trial, BAROQUE,<sup>22</sup> the percentage of ACR20 responders in the placebo group was notably higher than that observed in BAROQUE.<sup>22</sup> The reasons for the high placebo response are unknown. Similar to a study of atacecept,<sup>26</sup> the ACR20 response varied by region; however, regions with a high proportion of placebo responders tended to also have a high proportion of otilimab responders, and therefore the effect of otilimab versus placebo on ACR20 response was generally consistent across regions. The ACR20 response with sarilumab was significantly greater than placebo, was consistent with previous sarilumab trials<sup>27–29</sup> and sarilumab demonstrated superiority to both otilimab doses in the primary and secondary end points.

Pain in RA is multifactorial with both inflammatory and non-inflammatory causes contributing to the pain experienced by patients.<sup>30</sup> Targeting pain was a key component of the rationale for the contrASt programme, following a suggested benefit in pain relief in BAROQUE, despite non-significant DAS28-CRP <2.6 responses.<sup>22</sup> In contrASt 3, it was surprising that pain VAS scores were only marginally improved with either otilimab dose versus placebo, while



**Figure 4** LS mean CFB in (A) HAQ-DI, (B) CDAI total score, (C) FACIT-Fatigue and (D) pain VAS score, at weeks 12 and 24. CDAI, Clinical Disease Activity Index; CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; PBO, placebo; Q2W, once every 2 weeks; QW, once weekly; SE, standard error; VAS, Visual Analogue Scale.

significant improvements were reported with sarilumab, consistent with previous trials.<sup>27–29</sup> The reduction in pain with sarilumab may be due to the significant anti-inflammatory effects associated with this MoA, including the reduction of the marker of systemic inflammation, CRP<sup>31</sup> which was demonstrated with sarilumab, but not with otilimab, in this trial, despite the ~20%–30% reduction in IL-6 observed with otilimab. While it could be hypothesised that the otilimab dosing strategy used in this trial was insufficient to affect the pain pathway, the steady state serum otilimab concentrations reported were higher than had been predicted for this regimen.<sup>32</sup> Furthermore, serum otilimab concentrations achieved at week 12 with otilimab 90 mg and 150 mg once weekly were 2-fold and 3.5-fold higher than those achieved with otilimab 180 mg every 2 weeks in BAROQUE.<sup>22</sup> Nevertheless, significant improvements in pain VAS were reported in BAROQUE despite non-significant CRP reductions,<sup>22</sup> thus negating the hypothesis of underdosing.

Serum otilimab concentrations were proportionally (1.7-fold) higher with otilimab 150 mg than otilimab 90 mg and GM-CSF-otilimab complex accumulation suggested near-complete target engagement in the circulation. Accordingly, and consistent with BAROQUE,<sup>33</sup> a reduction in serum

concentrations of the putative PD biomarker for anti-GM-CSF activity, CCL17, was observed with both otilimab doses by week 1, and reduction continued to ~30%–40% at week 12, indicating that otilimab was pharmacologically active. Otilimab treatment also reduced C1M concentrations by ~10%, suggesting a reduction in joint tissue inflammation with otilimab.

It is worth noting that this trial included patients with a prolonged disease duration, which was similar to the patient population of a previous sarilumab trial,<sup>28</sup> but longer than the populations in previous anti-GM-CSF trials.<sup>18–19–22</sup> Additionally, nearly a third of patients had failed one or more previous JAKi. The results of this trial support those of an observational study demonstrating that sarilumab reduced disease activity in JAKi-IR patients,<sup>34</sup> but do not support the use of otilimab in this patient population. As both GM-CSF and IL-6 signal via the JAK pathway,<sup>35</sup> it is unlikely that the inclusion of JAKi non-responders would have had more of an impact on the response to otilimab than to sarilumab. Given the heterogeneity of patients with RA due to genetic, epigenetic and environmental factors, differential disease pathology, as well as the stage of disease progression including pannus formation and chronic



Table 3 Safety summary

Adverse event, n (%)	Pooled placebo (n=79)	Otilimab 90 mg once weekly (n=156)	Otilimab 150 mg once weekly (n=158)	Sarilumab 200 mg once every 2 weeks (n=156)
<b>Weeks 0–12</b>				
Any AE	37 (47)	65 (42)	63 (40)	72 (46)
Any SAE	2 (3)	4 (3)	1 (<1)	5 (3)
Any AESI	0 (0)	11 (7)	7 (4)	24 (15)
Serious infection*	0 (0)	1 (<1)	0 (0)	1 (<1)
Serious infection, excluding COVID-19*	0 (0)	0 (0)	0 (0)	0 (0)
Latent TB*	0 (0)	0 (0)	0 (0)	0 (0)
TB reactivation*	0 (0)	0 (0)	0 (0)	0 (0)
PAP*	0 (0)	0 (0)	0 (0)	0 (0)
COVID-19 diagnosis†	4 (5)	4 (3)	3 (2)	6 (4)
Any adjudicated CV event	1 (1)	0 (0)	0 (0)	0 (0)
Adjudicated MACE	1 (1)	0 (0)	0 (0)	0 (0)
VTE (DVT and/or PE)	0 (0)	0 (0)	0 (0)	0 (0)
DVT only	0 (0)	0 (0)	0 (0)	0 (0)
PE only	0 (0)	0 (0)	0 (0)	0 (0)
Any malignancy	0 (0)	1 (<1)	0 (0)	1 (<1)
Any malignancy, excluding NMSC	0 (0)	0 (0)	0 (0)	1 (<1)
Fatal SAE	0 (0)	1 (<1)	0 (0)	0 (0)
<b>Weeks 0–24‡</b>				
Any AE		92 (59)	99 (63)	98 (63)
Any SAE		8 (5)	1 (<1)	12 (8)
Any AESI		16 (10)	15 (9)	33 (21)
Serious infection		4 (3)	0 (0)	2 (1)
Serious infection, excluding COVID-19		2 (1)	0 (0)	0 (0)
Latent TB		0 (0)	4 (3)	2 (1)
TB reactivation		0 (0)	0 (0)	0 (0)
PAP		0 (0)	0 (0)	0 (0)
COVID-19 diagnosis†		8 (5)	7 (4)	8 (5)
Any adjudicated CV event		0 (0)	0 (0)	0 (0)
Adjudicated MACE		0	0	0
VTE (DVT and/or PE)		0 (0)	0 (0)	0 (0)
DVT only		0 (0)	0 (0)	0 (0)
PE only		0 (0)	0 (0)	0 (0)
Any malignancy		1 (<1)	0 (0)	1 (<1)
Any malignancy, excluding NMSC		0 (0)	0 (0)	1 (<1)
Fatal SAE		1 (<1)	0 (0)	1 (<1)

\*Only select AESIs with relevance to the MoA of otilimab or sarilumab are reported. See online supplemental table 9 for all AESIs.

†Total cases (either AEs or SAEs).

‡Data reported for patients who were randomised to active treatments from baseline. See online supplemental table 6 for the safety summary for patients who switched from placebo to active treatment at week 12.

AE, adverse event; AESI, adverse event of special interest; CV, cardiovascular; DVT, deep vein thrombosis; MACE, major adverse cardiovascular event; MoA, mechanism of action; NMSC, non-melanoma skin cancer; PAP, pulmonary alveolar proteinosis; PE, pulmonary embolism; SAE, serious adverse event; TB, tuberculosis; VAS, Visual Analogue Scale; VTE, venous thromboembolism.

synovial inflammation at treatment initiation,<sup>36–38</sup> it is plausible that GM-CSF is not a key driver of RA disease in this patient population. Whether a specific patient population may benefit from GM-CSF-targeting therapies remains to be seen, but to date, no other anti-GM-CSF/R therapies have progressed beyond phase II.

AEs were balanced across the treatment groups and SAEs were low. Previously, there were theoretical safety concerns surrounding anti-GM-CSFs due to the role of GM-CSF in the regulation of lung surfactant clearance.<sup>39–40</sup> Similarly, there were concerns of impairment of immunological responses, leading to TB reactivation.<sup>41–42</sup> Therefore, during the early development phase of otilimab, a maximum dose

was mandated by regulators and potential adverse effects including serious infection and PAP were closely monitored but low rates of serious infection and no events of PAP were reported.<sup>22–33</sup> Similarly, in contrAst 3, low rates of serious infection were reported, which were mainly attributed to COVID-19, and no events of TB reactivation or PAP were reported in either dose group. Furthermore, no MACE, VTE or PE were reported in any treatment group and neither of the two deaths were related to treatment as per investigator's judgement. These safety results add to those of prior otilimab and anti-GM-CSF RCTs.<sup>18–19–22–43–44</sup>

To our knowledge, this is the first phase III RCT in RA to randomise JAKi-IR patients for the primary endpoint analysis, and therefore provides a unique insight into the treatment response of this patient population. The robustness of the trial design and delivery is demonstrated by the consistency of the results from this trial with those of previous sarilumab trials.<sup>18–27–28</sup> The COVID-19 pandemic spanned the majority of the trial duration, and while recruitment was paused for 3 months to accommodate local restrictions, the overall impact on the trial was minimal, with a low number of protocol deviations and missing data points. Other strengths of the trial were the inclusion of a regionally diverse patient population due to conducting the trial in multiple countries. Additionally, outcomes considered important to patients<sup>45–47</sup> were captured including pain and its impacts, as well as physical function, fatigue, sleep disturbance and health-related quality of life. However, the trial length and absence of radiographic progression as an end point may have limited the overall interpretation of the findings, had efficacy in other end points been observed. The stratification factors resulted in a heterogeneous JAKi-IR subgroup comprising patients with single JAKi failure, multiple JAKi failures or a mix of bDMARD and JAKi failures. Additionally, the number of patients with prior anti-TNF failure was not captured, which may have provided further insight.

The contrAst programme included two other phase III RCTs, contrAst 1 and contrAst 2, that had a similar trial design to contrAst 3, but a longer trial duration (52 weeks), a different active comparator (tofacitinib), different background DMARDs (MTX only or csDMARDs) and a different patient population (MTX-IR only or cs/bDMARD-IR). Both RCTs met the primary end point of ACR20 vs placebo and improved some secondary end points (published separately). Therefore, while otilimab failed to meet the primary end point in contrAst 3, or demonstrate non-inferiority to the active comparators in the three RCTs, the totality of data does not entirely discount GM-CSF as a target or co-target in the treatment of RA and the results obtained may help to inform future clinical trial designs and influence the development of future therapeutic approaches in RA.

## CONCLUSIONS

In this treatment refractory patient population, otilimab failed to meet the primary end point of ACR20 response versus placebo at week 12 and most of the predefined secondary end points were not reached. As otilimab was demonstrated to be no different to placebo and less effective than sarilumab in this trial, and less effective than tofacitinib in contrAst 1 and contrAst 2, otilimab is unlikely to be a valuable addition to the current therapeutic armamentarium for RA.

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**Acknowledgements** The authors would like to thank Katherine Davy, Mark Layton and Jatin Patel for their support in the design of the trial. Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Clare Cunningham, PhD, Frankie Wignall, PhD and Chrystelle Rasamison of Fishawack Indicia, UK, part of Fishawack Health.

**Contributors** PCT, MEW, VS, MW, DS, SW, LAS, DB, JES, AG and RMF contributed to trial conception or design and data analysis or interpretation. PCT is acting as guarantor. TA and RMF contributed to data acquisition. IBMcl, TT, RW, JD, MB, CS, CO'S, CG and SM contributed to data analysis or interpretation. All authors contributed to drafting, or critically revising the article and provided final approval and agreement of accountability.

**Funding** This trial was funded by GlaxoSmithKline (GSK ID: 202018; NCT04134728).

**Competing interests** PCT has received consulting fees from AbbVie, Biogen, Bristol Myers Squibb, Fresenius, Galapagos, Gilead Sciences, GSK, Janssen, Lilly, Nordic Pharma, Pfizer, Roche, Sanofi and UCB, and research support from Galapagos. MEW receives research support from AbbVie, Aqual, Bristol Myers Squibb and Lilly, and consultation fees from AbbVie, Aclaris, Amgen, Bayer, Bristol Myers Squibb, Corvitas, Genosco, Gilead Sciences, GSK, Horizon, Johnson & Johnson, Lilly, Novartis, Pfizer, Rami Therapeutics, R Pharma, Roche, Sanofi, Scipher, Sci Rhom, Set Point and Trembeau. He holds stock/stock options of CanFite, Inmedix and Scipher. IBMcl has received consultancy and research support from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Causeway, Compugen, Gilead Sciences, GSK, Lilly, Novartis, Pfizer and UCB and holds a leadership role in Evelo, University of Glasgow, Versus Arthritis and is an NHS GGC Board Member and an *Annals of the Rheumatic Diseases* Editorial Board Member. TA has accepted research grants and/or honoraria for meetings from AbbVie, Alexion, Astellas Pharma, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Gilead Sciences, GSK, Lilly Japan, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Pfizer, Takeda Pharmaceutical and UCB Japan. VS has received consulting fees from AbbVie, Alpine, Alumis, Amgen, Aria, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Erismium, Genentech/Roche, GSK, Horizon, Inmedix, Janssen, Kiniksa, Lilly, Merck, MiMedx, Novartis, Omeros, Pfizer, R-Pharm, RAPT, Regeneron, Samsung, Sandoz, Sanofi, Scipher, Setpoint, Sorrento, Spherix, Tonix and Urica. TT received payment or honoraria from AbbVie, Asahi Kasei, Astellas, AstraZeneca, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Gilead Sciences, Janssen, Lilly Japan, Mitsubishi-Tanabe, Pfizer Japan and is an *Annals of the Rheumatic Diseases* Editorial Board Member. MB, DB, JD, CG, AG, SM, CO'S, DS, LAS, CS, JES, MW, RW and SW are employees of GSK and hold GSK stock/shares. RMF has received research support from AbbVie, Amgen, Arthroci, AstraZeneca, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Galvani, Genentech/Roche, Gilead, GSK, Janssen, Lilly, Novartis, Pfizer, Priovant, Samsung, Sanofi-Genzyme, Selecta and UCB; consulting fees from AbbVie, Amgen, Arthroci, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Galapagos, Galvani, Gilead, GSK, Janssen, Lilly, Novartis, Pfizer, Priovant, Samsung and UCB and honoraria from AbbVie, GSK and Pfizer and is an *Annals of the Rheumatic Diseases* Editorial Board Member.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Methods' section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** The protocol was approved by relevant Institutional Review Boards/Independent Ethics Committees (provided in the online supplemental

table 1). The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation, Good Clinical Practice and applicable country-specific regulatory requirements. Written informed consent was obtained from all patients.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Anonymised individual participant data and study documents can be requested for further research from <https://www.gsk-studyregister.com/en/>.

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## SUPPLEMENTARY MATERIALS

### Inclusion criteria

Patients were eligible to be included in the trial only if all of the following criteria applied:

1. Age  $\geq 18$  years at the time of signing informed consent.
2. Meets ACR/EULAR 2010 RA Classification Criteria with a duration of RA disease of  $\geq 6$  months at time of screening and patient not diagnosed before 16 years of age.
3. Must have active disease at both screening and baseline, as defined by having both:
  - A)  $\geq 6/68$  TJC, and
  - B)  $\geq 6/66$  SJC.

If surgical treatment of a joint has been performed, that joint cannot be counted in the TJC or SJC for enrolment purposes.

4. Must have a hsCRP measurement  $\geq 3$  mg/L at screening.
5. Must meet Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA.
6. Must have inadequate response, despite currently taking at least one and at most two concomitant csDMARDs for at least 12 weeks prior to Day 1 from the following:
  - A) MTX: weekly 15–25 mg oral or injected, for at least 12 weeks at the maximum tolerated dose prior to Day 1, with no change in route of administration in this time. A lower dose of  $\geq 7.5$  mg/week is acceptable if reduced for reasons of intolerance to MTX, for example, nausea/vomiting, hepatic or haematologic toxicity, or per local requirement (there must be clear documentation in the medical record). Exception: A lower dose of 6 mg/week is allowed if the minimum locally approved or recommended dose is lower than 7.5 mg/week.
  - B) Hydroxychloroquine up to 400 mg/day or chloroquine up to 250 mg/day.
  - C) Sulfasalazine up to 3000 mg/day.



- D) Leflunomide up to 20 mg/day. Note: concomitant use of leflunomide and MTX is not allowed, for safety reasons.
- E) Bucillamine up to 100 mg/day (or up to 300 mg/day if permitted per local requirements).
- F) Iguratimod up to 50 mg/day.
- G) Tacrolimus up to 3 mg/day

NOTE: The dose of csDMARD(s) must be stable and tolerated for at least 8 weeks prior to Day 1 and should remain stable throughout the trial from screening to end of treatment period, except adjustment for safety reasons.

- 7. Must have inadequate response to at least one bDMARD at an approved dose and/or at least one JAKi at an approved dose. In both cases this may be with or without combination with a csDMARD. Prior bDMARD or JAKi therapy must be discontinued before randomisation per the **Supplementary Table 2**.
- 8. Body weight  $\geq 40$  kg
- 9. Male or female patients are eligible to participate so long as they meet and agree to abide by the contraceptive criteria
- 10. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in the protocol.
- 11. For patients on MTX: Must be willing to continue or initiate treatment at screening, with oral folic acid (at least 5 mg/week) or equivalent and be treated during the entire trial (mandatory co-medication for MTX treatment).

### Exclusion criteria

A patient will not be eligible for inclusion in this trial if any of the following criteria apply:

- 1. Active infections (including localised infections), or history of recurrent infections (excluding recurrent fungal infections of the nail bed), or has required management of acute or chronic infections, as follows:
  - Currently taking any suppressive anti-infective therapy for a chronic infection (such as pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria) OR

- Hospitalisation for treatment of infection within 26 weeks of Day 1 OR
  - Use of parenteral intravenous or intramuscular antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 26 weeks of Day 1 or oral antimicrobials (apart from isonicotinic acid hydrazide use for latent TB treatment) within 14 days of Day 1.
2. Symptomatic herpes zoster within 3 months prior to screening.
  3. Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
  4. Known infection with human immunodeficiency virus or positive test at screening.
  5. History of infected joint prosthesis at any time, with the prosthesis still in situ. History of chronic leg ulcers, permanent in-dwelling catheters, chronic sinusitis, recurrent chest infections or recurrent urinary tract infections.
  6. Any baseline symptomatology that in the investigator's opinion would confound the early detection of pulmonary alveolar proteinosis based upon clinical features, such as persistent cough (Common Terminology Criteria Grade  $\geq 2$ ) or persistent dyspnoea (dyspnoea scale Grade  $\geq 2$ ).
  7. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.
  8. Current acute or chronic Hepatitis B and/or Hepatitis C.
  9. Current or history of renal disease or estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation calculation  $< 60$  mL/min/1.73m<sup>2</sup> at screening.
  10. Breast cancer within the past 10 years or lymphoma, leukaemia, or any other malignancy within the past 5 years except for cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease, or basal cell or squamous epithelial cancers of the skin that have been resected with no evidence of recurrence or metastatic disease for at least 3 years.
  11. History of any lymphoproliferative disorder, such as Epstein–Barr Virus-related lymphoproliferative disorder, or signs and symptoms suggestive of current lymphatic disease.
  12. History or presence of significant other concomitant illness according to the Investigator judgment such as, but not limited to cardiovascular (including Stage

III or IV cardiac failure according to New York Heart Association classification, myocardial infarction within 3 months, unstable angina pectoris, uncontrolled hypertension, uncontrolled hypercholesterolemia), neurological, endocrinological, gastrointestinal (including diverticulitis), hepatic disease, metabolic, lymphatic disease, or previous renal transplant that would adversely affect the patient's participation in the trial.

13. Any condition or contraindication as addressed in the local product information or local clinical practice for sarilumab that that would preclude the patient from participating in the trial.
14. History of other inflammatory rheumatologic or systemic autoimmune disorder, other than Sjögren's syndrome secondary to RA, that may confound the evaluation of the effect of the trial intervention such as mixed connective tissue disease, psoriatic arthritis, juvenile chronic arthritis, spondyloarthritis, Felty Syndrome, systemic lupus erythematosus, scleroderma, Crohn's disease, ulcerative colitis, or vasculitis.
15. Presence of fibromyalgia that, in the investigator's opinion, would make it difficult to appropriately assess RA activity for the purposes of the trial.
16. Undergone any major surgery within 8 weeks prior to trial entry or will require major surgery during the trial that, in the opinion of the investigator in consultation with the medical monitor, would pose an unacceptable risk to the patient.
17. Current or previous active *Mycobacterium tuberculosis* (TB) regardless of treatment.
18. Evidence of latent TB (as documented by a positive QuantiFERON-TB Gold plus test or T-SPOT.TB test at screening, no findings on medical history or clinical examination consistent with active TB, and a normal chest radiograph) except for patients that either:
  - Are willing to complete at least 4 weeks of anti-TB therapy as per World Health Organization (WHO) or national guidelines prior to randomisation and agree to complete the remainder of treatment while in the trial OR
  - Are documented as having evidence of satisfactory anti-TB treatment as per WHO or national guidelines within the last 5 years following review by a physician specialising in TB.

19. Previous close contact with a person with active TB and did not receive satisfactory anti-TB treatment as per WHO or national guidelines.
20. Significant allergies to humanised mAbs or known hypersensitivity to sarilumab or any of its active ingredients.
21. Clinically significant multiple or severe drug allergies or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
22. Any prior treatment antagonising GM-CSF or its receptor.
23. Any prior treatment with anti-IL-6 or IL-6R antagonists (including but not limited to sarilumab and tocilizumab).
24. Patients who are expected to be non-compliant with restrictions on medications and vaccinations prior to the trial, during the trial or during the 8-week safety follow-up of the trial. See **Supplementary Table 2** for details of prohibited medications/treatments.
25. Current enrolment or past participation within the last 42 days before randomisation in any other clinical trial involving an investigational trial treatment or any other type of medical research.
26. Alanine transferase (ALT) or aspartate transaminase (AST)  $>1.5 \times$  upper limit of normal (ULN).
27. Bilirubin  $>1.5 \times$  ULN (isolated bilirubin  $>1.5 \times$  ULN is acceptable if bilirubin is fractionated and direct bilirubin  $<35\%$ ).
28. Has a positive test for hepatitis B (HBV) defined as either:
  - Positive for hepatitis B surface antigen OR
  - Positive for hepatitis B core antibody and positive for HBV deoxyribonucleic acid.
29. Positive test for hepatitis C antibody at screening. Patients with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained.
30. Haemoglobin  $\leq 9$  g/dL; white blood cell count  $\leq 3.0 \times 10^9$ /L; platelet count  $\leq 100 \times 10^9$ /L; absolute neutrophil count  $<1.0 \times 10^9$ /L; lymphocyte count  $\leq 0.75 \times 10^9$ /L at screening.



31. Abnormal chest radiograph within 12 weeks of screening judged by the investigator as clinically significant.
32. Pregnant or lactating, or women planning to become pregnant or initiating breastfeeding.
33. Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within a year prior to Day 1.
34. History of sensitivity to any of the trial treatments, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

## Handling of missing data

Intermittent missing data (i.e. between two non-missing assessments) for the ACR20 response were imputed under a missing at random (MAR) assumption.

If a participant experienced any of the intercurrent (post-randomisation) events (IEs\*) but efficacy data continued to be collected, their data were analysed as if they were still on the original randomised intervention.

Trial withdrawal before the completion of the trial created missing outcome data. This could occur concurrently or after the IE.

Missing data for the ACR20 response resulting from trial withdrawal were imputed using one of three possible multiple imputation (MI) models depending on the availability of off-treatment data (i.e. data that were collected post discontinuation of trial intervention), using principles introduced by Roger et al.<sup>1</sup>

### 1. MI using off-treatment data within randomised treatment arm:

If there was sufficient off-treatment data within a randomised treatment arm (i.e. at least 3 participants per arm per visit), then missing data were imputed conditional on the participant's observed outcomes, using off-treatment data within randomised treatment arm. The use of this MI model assumed that missing outcomes resulting from participants withdrawing from the trial would behave in a similar way to other participants who discontinued trial intervention, were randomised to the same treatment arm, and continued providing data post-discontinuation of trial intervention.

### 2. MI using off-treatment data across all treatment arms:

If there was insufficient off-treatment data within a randomised treatment arm (i.e. failure of the imputation model in option 1) but there was sufficient off-treatment data across all treatment arms combined (i.e. at least 3 participants per visit), then missing data were imputed conditional on the participant's observed outcomes, using off-treatment data across all treatment arms. The use of this MI model assumed that missing outcomes resulting from participants withdrawing from the trial would behave in a similar way to other participants who discontinued trial intervention and continued providing data post-discontinuation of trial intervention regardless of randomised treatment arm.

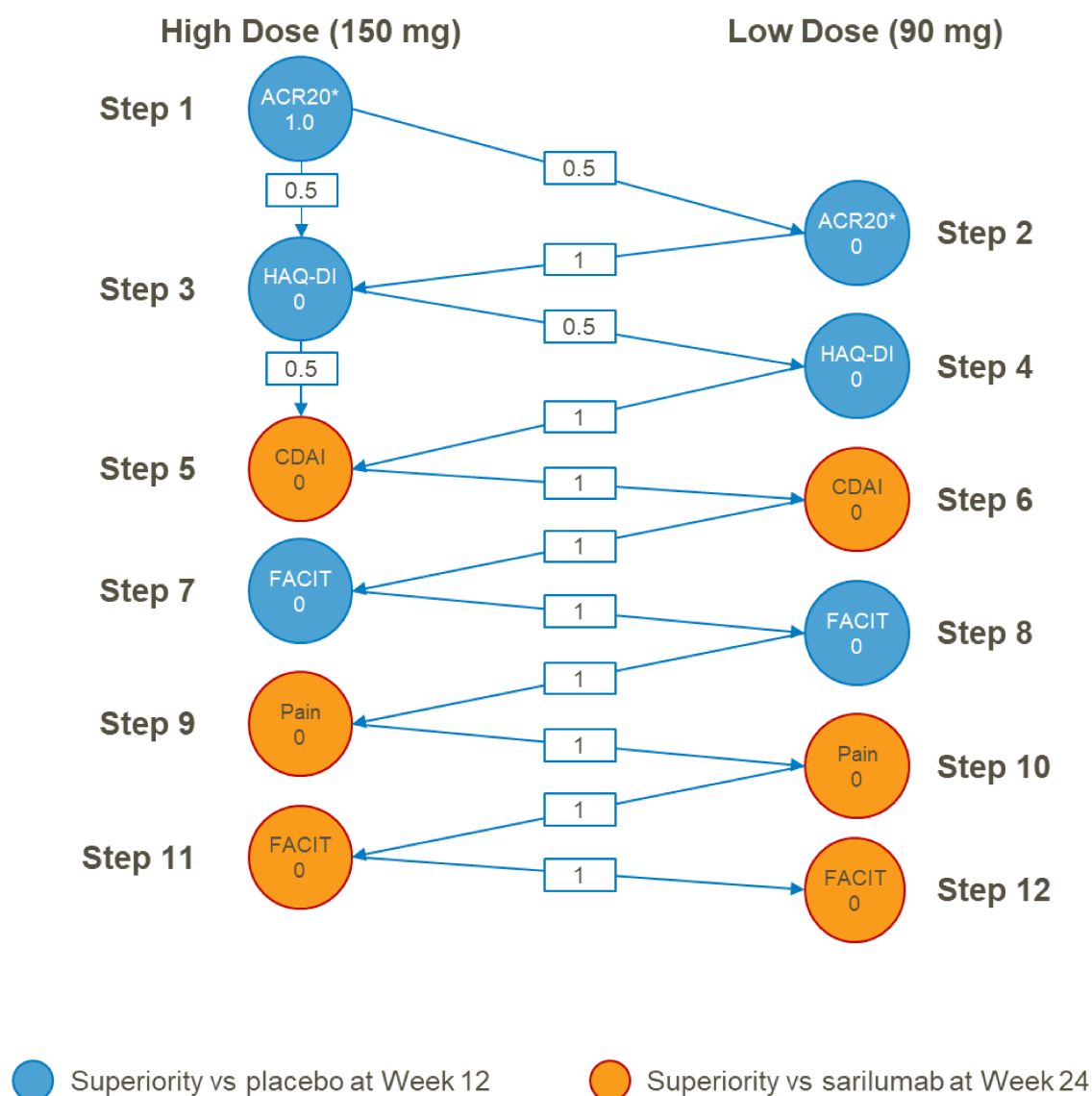
### 3. MI under MAR assumption:

If there was insufficient off-treatment data (i.e. neither option 1 nor 2 were feasible) then all missing data were imputed under a MAR assumption. This MI model used all available data collected on- and off-treatment within randomised treatment arm and assumed missing outcomes resulting from participants withdrawing from the trial would behave in a similar way to participants who were randomised to the same treatment arm and had data collected in the trial, with no adjustment for values before or after intercurrent events.

Note: Week 1 data were not included in any imputation models due to the unavailability of off-treatment data at this visit by design of the trial.

\*The IEs anticipated to impact on the interpretation of the treatment effect for the primary objective were: discontinuation of study intervention for any reason; use of prohibited medication and change in stable dose of background medication.

1. Roger JH, Bratton DJ, Mayer B, et al. Pharm Stat. 2019;18:85–95.

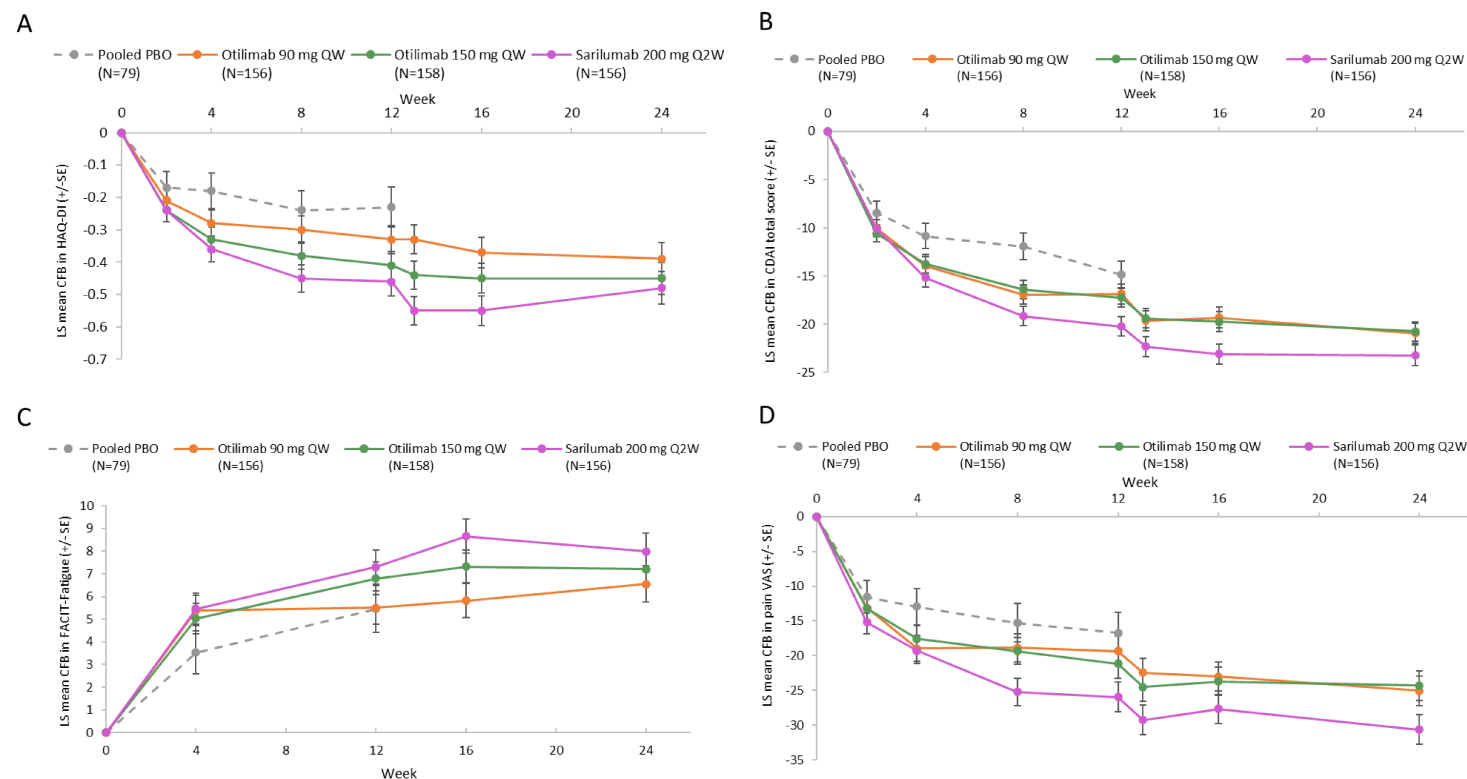
**Supplementary Figure 1. Multiple testing hierarchy**

\*Primary endpoint; numbers in the circles refer to the initial weighting of alpha; numbers along the arrows refer to the weighting of alpha which is passed along to the next test.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index.

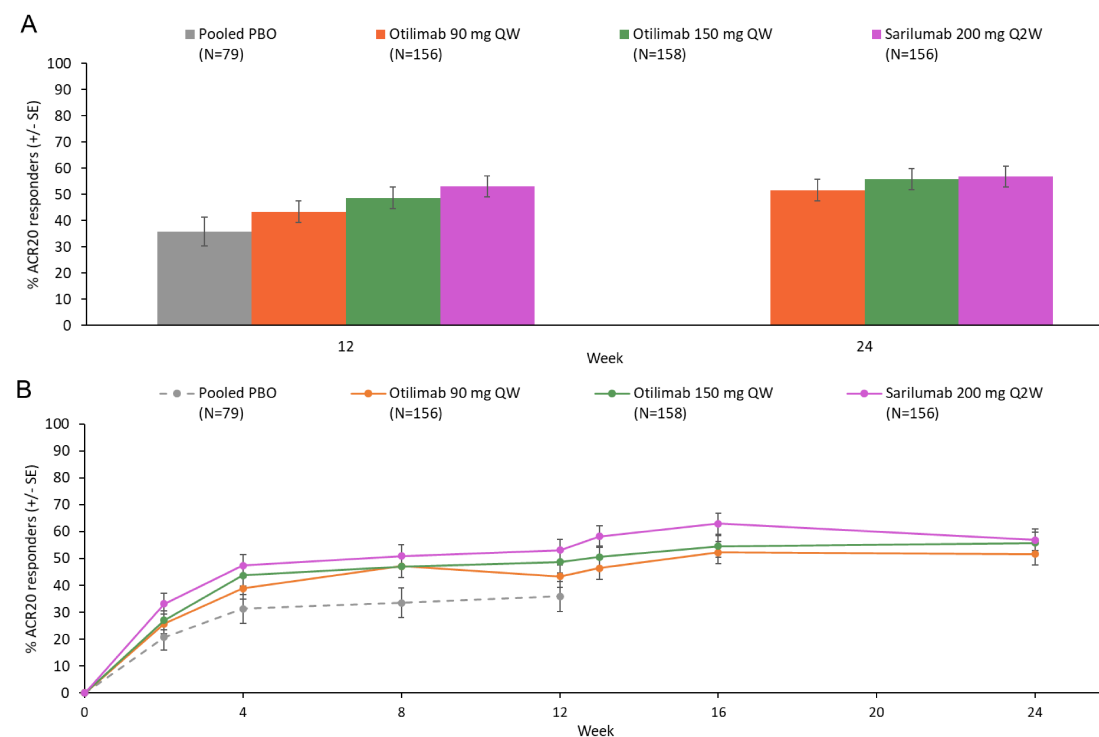


**Supplementary Figure 2.** LS mean change from baseline in major secondary endpoints A) HAQ-DI, B) CDAI total score, C) FACIT-Fatigue, and D) pain VAS score at each assessment visit



CDAI, Clinical Disease Activity Index; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; QW, once weekly; Q2W, once every 2 weeks; SE, standard error; VAS, Visual Analogue Scale.

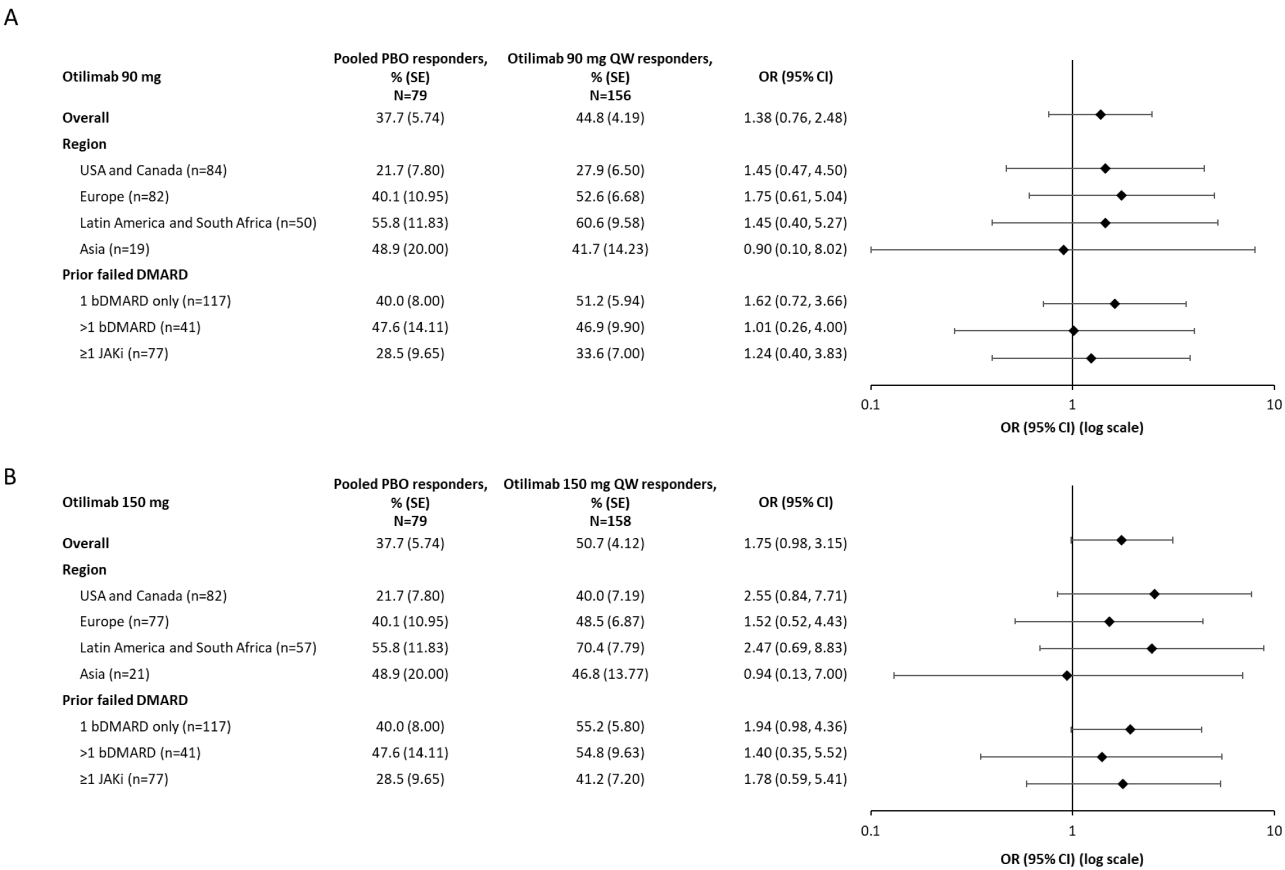
**Supplementary Figure 3.** Supplementary analysis of the proportion of patients achieving ACR20 at A) Week 12 and 24 and B) each assessment visit (non-responder imputation)



Secondary analysis of ACR20 response using non-responder imputation (patients who discontinued treatment were considered non-responders).

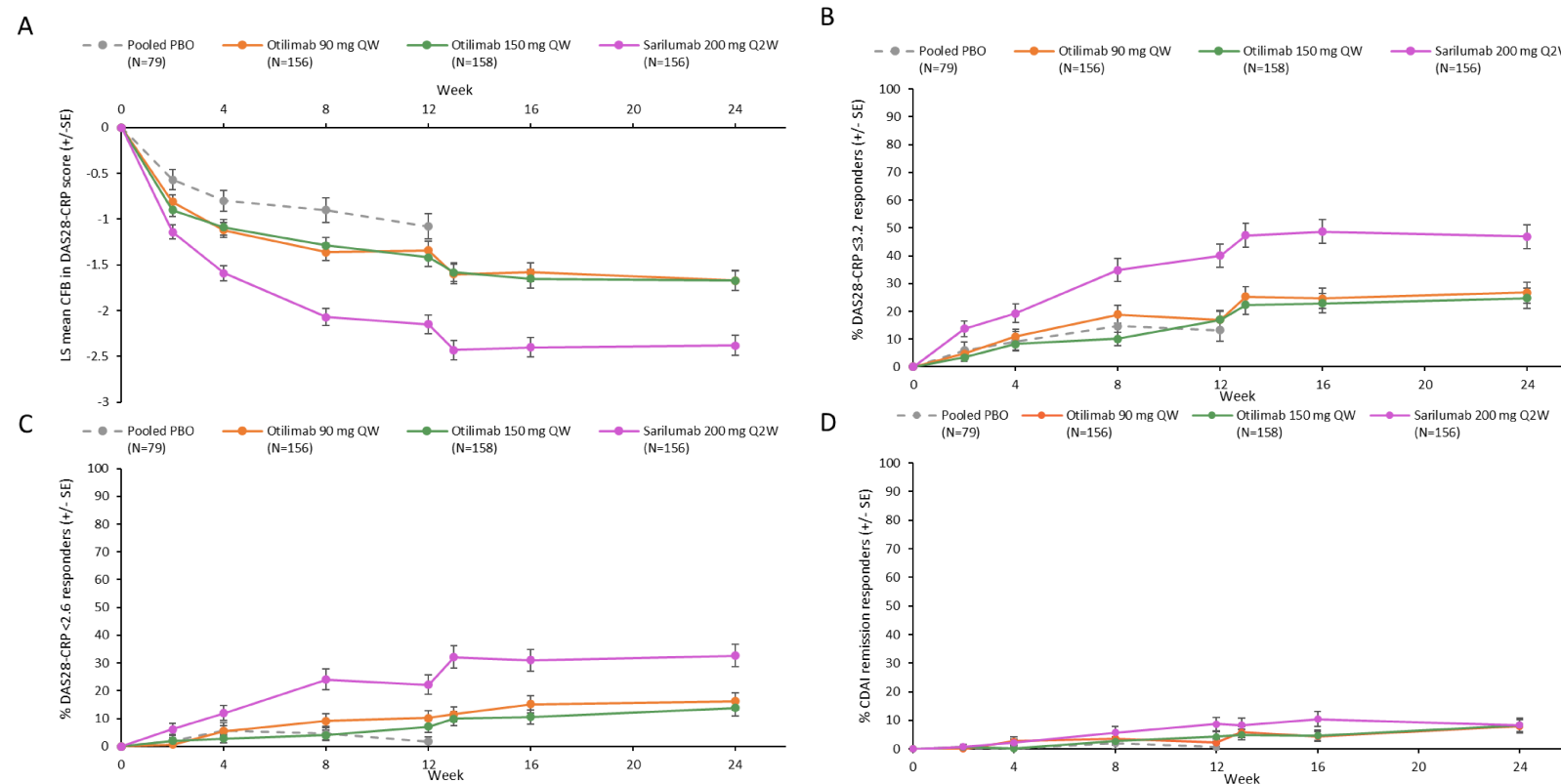
ACR, American College of Rheumatology; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; SE, standard error.

Supplementary Figure 4. ACR20 subgroup analysis for A) otilimab 90 mg and B) otilimab 150 mg at Week 12



ACR, American College of Rheumatology; (b)DMARD, (biologic) disease-modifying anti-rheumatic drug; CI, confidence interval; JAKi, Janus kinase inhibitor; OR, odds ratio; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; SE, standard error.

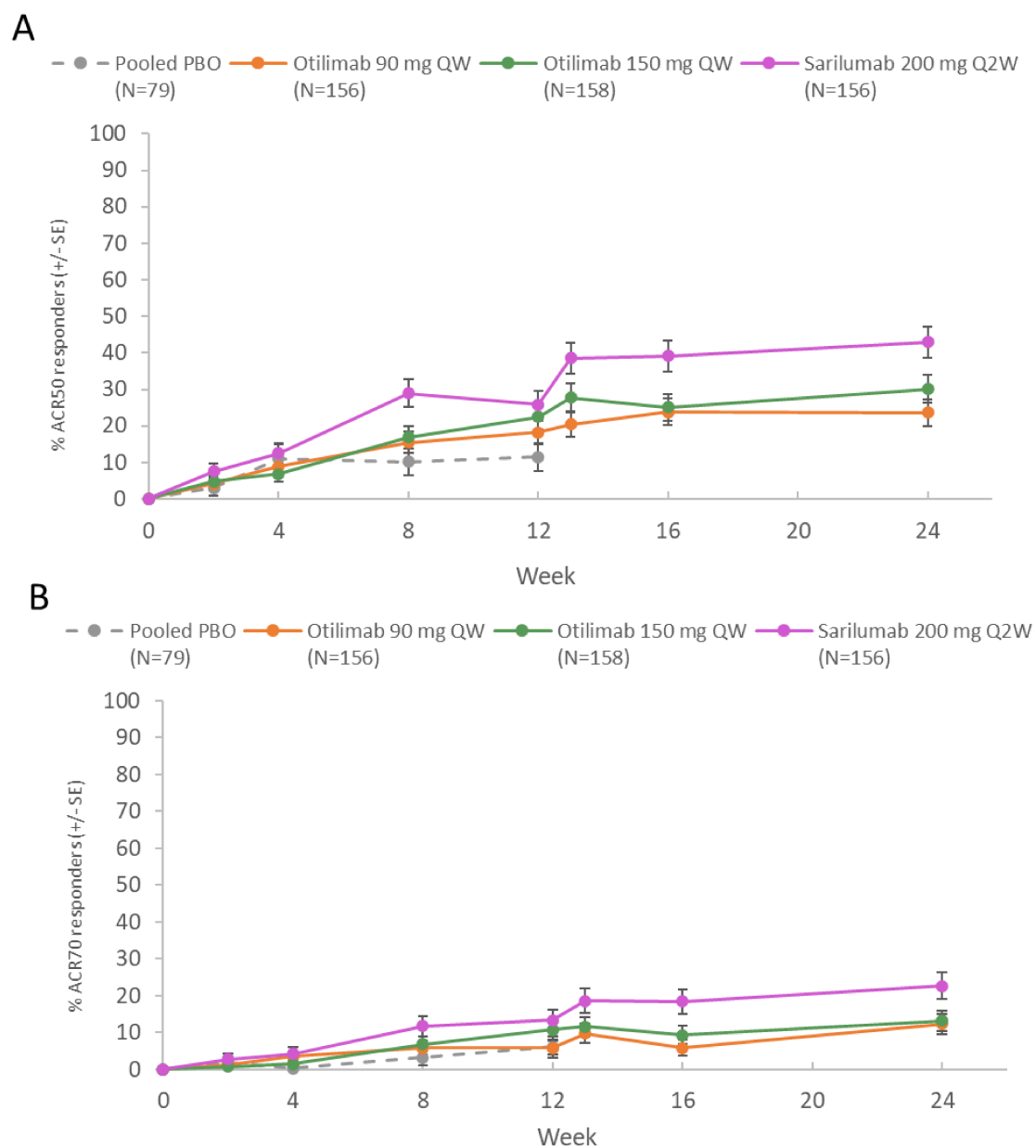
**Supplementary Figure 5.** A) LS mean change from baseline in DAS28-CRP, and proportion of patients achieving B) DAS28-CRP  $\leq 3.2$  C) DAS28-CRP  $< 2.6$  and D) CDAI remission ( $\leq 2.8$ ) at each assessment visit



CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score-28 joints; LS, least squares; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; SE, standard error; VAS, Visual Analogue Scale.

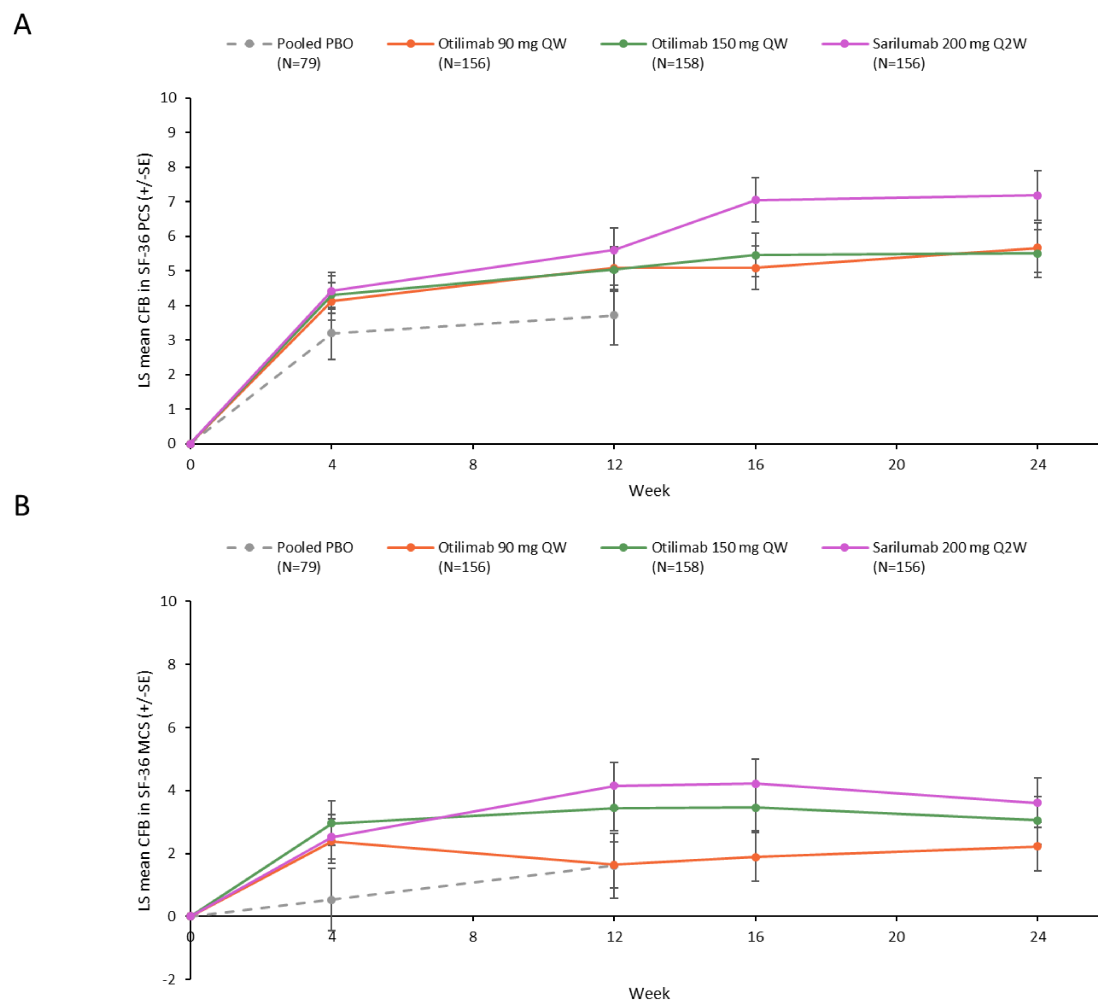


**Supplementary Figure 6.** Proportion of patients achieving A) ACR50 and B) ACR70 response at each assessment visit



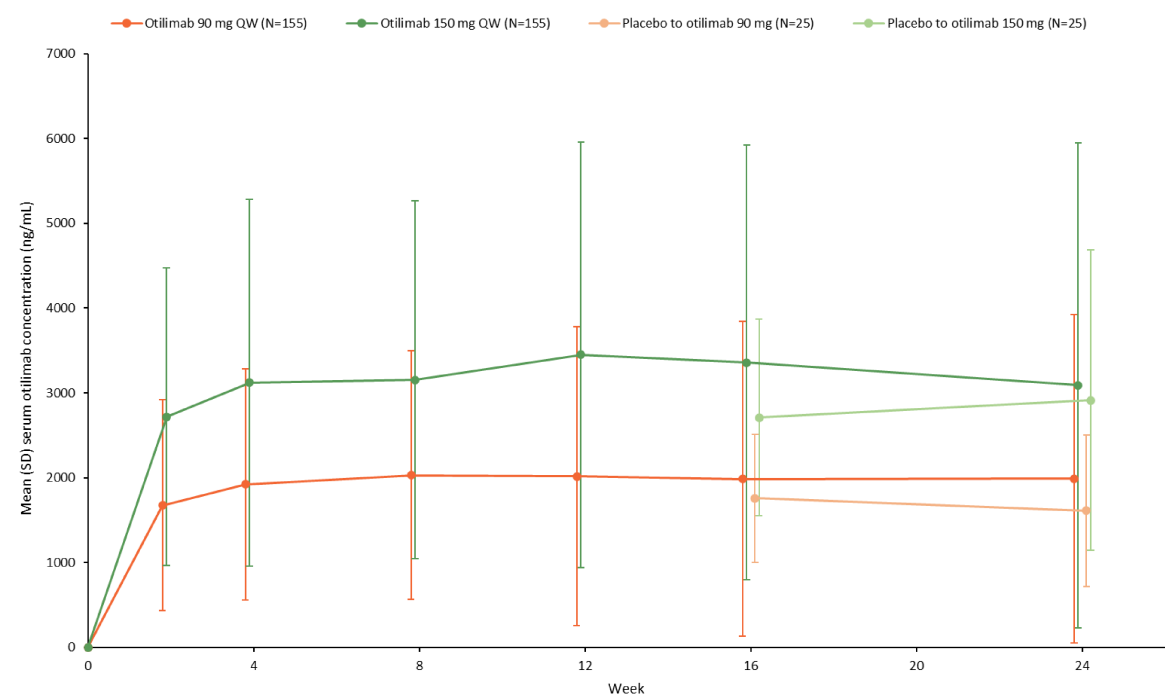
ACR, American College of Rheumatology; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; SE, standard error.

**Supplementary Figure 7.** Change from baseline in the SF-36 A) PCS and B) MCS at each assessment visit



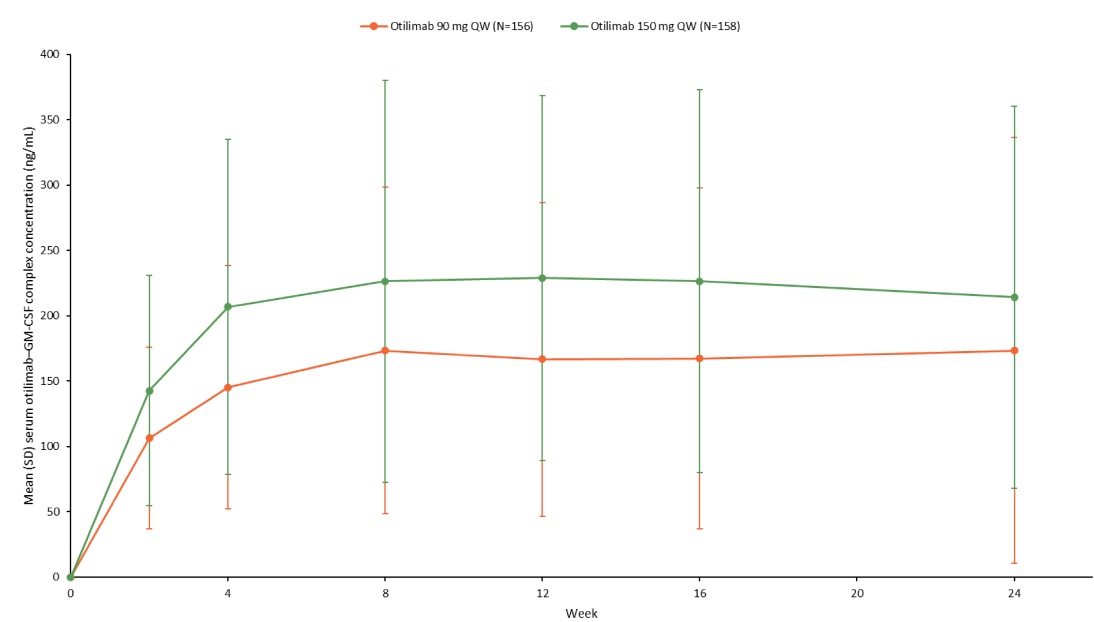
CFB, change from baseline; LS, least squares; MCS, Mental Component Summary; PCS, Physical Component Summary; QW, once weekly; Q2W, once every 2 weeks; SE, standard error; SF-36, Short Form-36 questions.

Supplementary Figure 8. Otilimab serum concentrations at each assessment visit



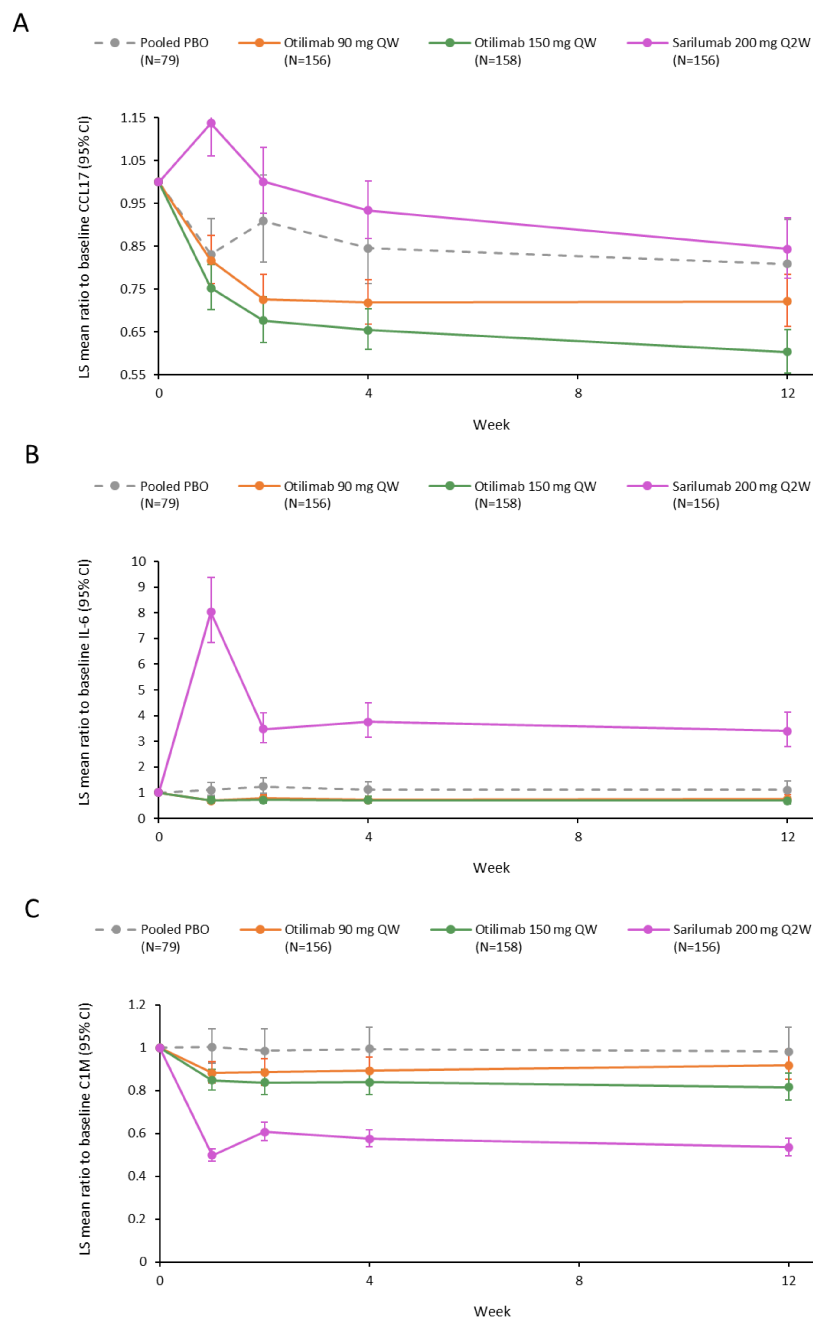
QW, once weekly; SD, standard deviation.

Supplementary Figure 9. Otilimab–GM-CSF complex accumulation over time



GM-CSF, granulocyte-macrophage colony-stimulating factor; SD, standard deviation; QW, once weekly.

**Supplementary Figure 10.** Change from baseline in A) CCL17, B) IL-6 and C) C1M up to Week 12



C1M, matrix-metalloprotease-degraded Type I collagen, CCL17, C-C motif chemokine ligand 17; CI, confidence interval; IL-6, interleukin 6; LS, least squares; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks.

**Supplementary Table 1.** List of investigators and trial sites

Description and address of research facility/hospital/institution	Name and address of IEC/IRB
<b>Argentina (N=104)</b>	
Clinica Adventista Belgrano, Estomba 1710, Ciudad Autonoma Buenos Aires, Buenos Aires, C1430EGF, Argentina	Comite Independiente De Etica Luis Maria Zieher, J .E Uriburu 774, Ciudadada Autonoma de Buenos Aires, Buenos Aires, 1111, Argentina
Hospital Militar Central "Cirujano Mayor Dr. Cosme Argerich", Reumatologia, Piso 4 Cons 418, Av. Luis M. Campos 726, Ciudad Autónoma de Buenos Aires, C1426BOR, Argentina	CIREC, A. Luis Maria Campos 726, Ciudad Autonoma de Buenos Aires, Ciudad Autonoma Buenos Aires, C1426BOR, Argentina
Mind Out Research, Jose Pedro Varela - 3901/3954, Ciudad Autonoma Buenos Aires, Buenos Aires, C1417, Argentina	IEC - Comité Independiente de Ética para Ensayos en Farmacología Clínica (FEFyM), Pte. J. E. Uriburu 774 1er Piso, Ciudadada Autonoma de Buenos Aires, Buenos Aires, C1027AAP, Argentina
Hospital Italiano de La Plata, Avenida 51 entre 29 y 30, La Plata, Buenos Aires, B1900AXI, Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Avenida de Mayo 869, Ciudad Autónoma de Buenos Aires, Buenos Aires, C1084AAD, Argentina
Instituto Medico de alta Complejidad San Isidro S.A (IMAC), Avenida Del Libertador 16.958, San Isidro, Buenos Aires, 1643, Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Avenida de Mayo 869, Ciudad Autónoma de Buenos Aires, Buenos Aires, C1084AAD, Argentina
Aprillus Asistencia e Investigación de Arcis Salud SRL, Avenue Corrientes 2554 2do piso, Ciudad Autonoma de Buenos Aires, Buenos Aires, C1046AAQ, Argentina	Comité Independiente de Ética para Ensayos en Farmacología Clínica (FEFyM), Pte. J. E. Uriburu 774 1er Piso, Ciudadada Autonoma de Buenos Aires, Buenos Aires, C1027AAP, Argentina
Fundacion Respirar, Av. Cabildo 1548 1° A, Ciudad Autonoma de Buenos Aires, Buenos Aires, 1426, Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (Argentina), Avenida de Mayo 869, Ciudad Autónoma de Buenos Aires, Buenos Aires, C1084AAD, Argentina
CER San Juan, Laprida 532, San Juan, San Juan, J5402DIL, Argentina	Comite Independiente De Etica Luis Maria Zieher, J .E Uriburu 774, Ciudadada Autonoma de Buenos Aires, Buenos Aires, 1111, Argentina
Sanatorio Parque S.A., Boulevard Orono 860, Rosario, Santa Fe, S2000DSV, Argentina*	Comite de etica en investigacion, Alvear 854, Rosario, Santa Fe, 2000, Argentina
CCBR - Buenos Aires - AR, Ruiz Huidobro 4693, Ciudad Autonoma Buenos Aires, Buenos Aires, C1430CKE, Argentina	Comite de Etica Saavedra, Avenue Ruiz Huidobro 4693, Caba, Buenos Aires, C1430CKE, Argentina
Instituto de Investigaciones Clinicas San Nicolas, Pellegrini 346, San Nicolas, Buenos Aires, B2900DMH, Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Avenida de Mayo 869, Ciudad Autónoma de Buenos Aires, Buenos Aires, C1084AAD, Argentina
Centro de Investigaciones Medicas Mar del Plata, Av.Colón 3083,1y 5to piso, Mar del Plata, Buenos Aires, B7600FYK, Argentina	Comité de Ética en Investigación - Centro de Investigaciones Médicas Mar del Plata, Av. Colón 3083, 1 y 5to piso, Mar del Plata, Buenos Aires, B7600FYK, Argentina
CIDIM-Centro Integral de Diagnóstico por Imágenes Marchegiani, Rondeau 293, 6to piso, Nueva Cordoba, X5000AVE, Argentina*	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Avenida de Mayo 869, Ciudad Autónoma de Buenos Aires, Buenos Aires, C1084AAD, Argentina
<b>Belgium (N=1)</b>	
CHU Ambroise Paré, Pharmacie, Boulevard Kennedy 2, Mons, 7000, Belgium	Comité d'Ethique du CHU Ambroise Paré, Boulevard Kennedy 2, Mons, 7000, Belgium



Description and address of research facility/hospital/institution	Name and address of IEC/IRB
<b>Canada (N=2)</b>	
Aggarwal and Associates Ltd, Room 201, 490 Bramalea Road, Brampton, Ontario, L6T 0G1, Canada	WIRB, 1019 39th Avenue SE, Suite 120, Puyallup, Washington, 98374, Canada
The Waterside Clinic, 125 Bell Farm Road., Barrie, Ontario, L4M 6L2, Canada*	WIRB, 1019 39th Avenue SE, Suite 120, Puyallup, Washington, 98374, Canada
Centre de Recherche Musculo- Squelettique, 1119 Ste. Marguerite Street, Trois-Rivieres, Québec, G8Z 1Y2, Canada	WIRB, 1019 39th Avenue SE, Suite 120, Puyallup, Washington, 98374, Canada
LMC Clinical Research dba Manna Research Inc. Burlington South, 2119 Lakeshore Road, Burlington, Ontario, L7R 1A4, Canada*	WIRB, 1019 39th Avenue SE, Suite 120, Puyallup, Washington, 98374, Canada
<b>Czechia (N=46)</b>	
MEDICAL PLUS s.r.o., Obchodni 1507, Uherske Hradiste, 686 01, Czechia	Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole, V Uvalu 84, Dermatovenelogicke oddeleni, Praha 5, 15006, Czech Republic
Fakultni nemocnice v Motole, V Uvalu 84, Prague, 150 06, Czechia*	Eticka komise Fakultni nemocnice v Motole pro multicentricka klinicka hodnoceni, V Uvalu 84, Praha 5, 15006, Czech Republic
Revmatologie s.r.o., Halasovo namesti 597/1, Brno, 638 00, Czechia	Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole, V Uvalu 84, Dermatovenelogicke oddeleni, Praha 5, 150 06, Czech Republic
Vesalion s.r.o., Bozdechova 619/6, Ostrava, 70200, Czechia	Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole, V Uvalu 84, Dermatovenelogicke oddeleni, Praha 5, 15006, Czech Republic
FNsP u sv. Anny v Brne, Pekarska 53, Brno, 65691, Czechia	Eticka komise Fakultni nemocnice u sv. Anny v Brne, Pekarska 53, Brno, 65691, Czech Republic
Affidea Praha s.r.o., Sustova 1930/2, Praha 11, 148 00, Czechia	Eticka komise Fakultni nemocnice v Motole pro multicentricka klinicka hodnoceni, V Uvalu 84, Praha 5, 150 06, Czech Republic
Revmatologicky ustav, Na Slupi 450/4, Praha 2, 128 50, Czechia	Eticka komise Revmatologicky ustav, Na Slupi, Praha 2, 12850, Czech Republic
PV-Medical s.r.o., Stefanikova 477, Zlin, 760 01, Czechia	Eticka komise Fakultni nemocnice v Motole pro multicentricka klinicka hodnoceni, V Uvalu 84, Praha 5, 150 06, Czech Republic
<b>Germany (N=12)</b>	
Rheumazentrum Ruhrgebiet, Claudiusstr. 45, Herne, Nordrhein- Westfalen, 44649, Germany*	Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster, Gartenstr. 210-214, Münster, 48147, Germany
Charite Universitaetsmedizin Berlin CCM, Chariteplatz 1, Berlin, Berlin, 10117, Germany*	Universität Leipzig, Ethik- Kommission, Käthe-Kollwitz-Str. 82, Leipzig, 4109, Germany
HRF Hamburger Rheuma Forschungszentrum, Moenckebergstrasse 27, Hamburg, Hamburg, 20095, Germany	Ärztekammer Hamburg Ethikkommission, Weidestraße 122 b, Hamburg, 22083, Germany

Description and address of research facility/hospital/institution	Name and address of IEC/IRB
Gem. Praxis Drs. Gauler und Fliedner, Moeserstr. 46, Osnabrueck, Niedersachsen, 49074, Germany*	Ärztchamber Niedersachsen Ethikkommission, Karl-Wiechert- Allee 18-22, Hannover, 30625, Germany
SMO.MD, Bierer Weg 9, Magdeburg, 39120, Germany	Ethik-Kommission des Landes Sachsen-Anhalt Geschäftsstelle, Kühnauer Street. 70, Dessau-Roßlau, 6846, Germany
Rheumazentrum Prof. Neeck, Goethestrasse 40, Bad Doberan, 18209, Germany*	Ethik-Kommission an der Medizinischen Fakultät Leipzig, Kaethe-Kollwitz-Str. 82, Leipzig, 04109, Germany
Universitätsklinikum Leipzig, Liebigstr. 20, Leipzig, Sachsen, 4103, Germany*	Geschäftsstelle der Ethik- Kommission an der Medizinischen Fakultät der Universität Leipzig, c/o Zentrale Poststelle, Liebigstraße 18, Leipzig, 4103, Germany
Studienzentrum Rendsburg, Hollesenstrasse 27a, Rendsburg, Schleswig-Holstein, 24768, Germany*	Landesamt für Gesundheit und Soziales Geschäftsstelle der Ethik- Kommission des Landes Berlin, Turmstr. 21, Berlin, 10559, Germany
<b>Hungary (N=6)</b>	
Revita Reumatologiai Rendelo, Margit krt. 50-52., Budapest, 1023, Hungary	Medical Research Council Ethics Committee for Clin Pharmacology (MRC ECCP), Széchenyi István tér 7-8, Budapest, H-1051, Hungary
Vital Medical Center, Jozsef Attila utca 17, Veszprem, H-8200, Hungary	Medical Research Council Ethics Committee for Clin Pharmacology (MRC ECCP), Széchenyi István tér 7-8, Budapest, H-1051, Hungary
Óbudai Egészségügyi Centrum Kft, Lajos utca 74-76., Budapest, 1036, Hungary*	Medical Research Council Ethics Committee for Clin Pharmacology (MRC ECCP), Széchenyi István tér 7-8, Budapest, H-1051, Hungary
Drug Research Center (DRC), Ady Endre str.12, Balatonfüred, 8230, Hungary	Medical Research Council Ethics Committee for Clin Pharmacology (MRC ECCP), Széchenyi István tér 7-8, Budapest, H-1051, Hungary
DRC Gyógyszervizsgáló Központ Kft., Ady Endre utca 12., Balatonfüred, 8230, Hungary*	Medical Research Council Ethics Committee for Clin Pharmacology (MRC ECCP), Széchenyi István tér 7-8, Budapest, H-1051, Hungary
<b>Italy (N=0)</b>	
ASST degli Spedali Civili di Brescia - Spedali Civili di Brescia, Reparto di Medicina Interna 2, Piazzale Spedali civili 1, Brescia, Lombardia, 25123, Italy*	Comitato Etico Provinciale della Provincia di Brescia, Gastroenterology, P.le Spedali Civili, 1, Brescia, 25123
Azienda Ospedaliera Universitaria Integrata Verona (Ospedale Borgo Trento), Reumatologia, Piazzale Aristide Stefani 1, Verona, Veneto, 37126, Italy*	Comitato Etico per la Sperimentazione Clinica delle Provincie di Verona e Rovigo, P.le Stefani, 1, Verona, 37126, Italy
Istituto Clinico Humanitas, U.O. Reumatologia ed Immunologia Clinica, Dipartimento di Medicina Interna, Via Manzoni 113, Rozzano, Lombardia, 20089, Italy*	Comitato Etico Milano Area 2, VIA ALESSANDRO MANZONI 56, Rozzano, Milano, 20089, Italy
<b>Japan (N=38)</b>	
Hokkaido University Hospital, North 14, West 5, Kita-ku, Sapporo-shi, Hokkaido, 060-8648, Japan	Hokkaido University Hospital Institutional Review Board, Kita-ku Kita 14jo Nishi 5, Sapporo-shi, Hokkaido, 060-8648, Japan

Description and address of research facility/hospital/institution	Name and address of IEC/IRB
Chubu Rosai Hospital, 1-10-6, Komei, Minato-ku, Nagoya-city, Aichi, 455- 8530, Japan	Review Board of Human Rights and Ethics for Clinical Studies IRB, Kyobashi 2-2-1, Chuo-ku, Tokyo-To, 104-0031, Japan
Daido Clinic, 8, Hakusui-cho, Minami- ku, Nagoya-city, Aichi, 457-8511, Japan	Kojunkai Daido Hospital Institutional Review Board, Minami-ku Hakusui-cho 9, Nagoya-shi, Aichi-Ken, 457-8511, Japan
National Hospital Organization Nagoya Medical Center, 4-1-1, Sannomaru, Naka-ku, Nagoya-city, Aichi, 460-0001, Japan*	NHO CRB, Higashigaoka 2-5-21, Meguro-ku, Tokyo-To, 152-8621, Japan
Hitachi, Ltd. Hitachinaka General Hospital, 20-1, Ishikawa-cho, Hitachinaka-city, Ibaraki, 312-0057, Japan	Review Board of Human Rights and Ethics for Clinical Studies IRB, Kyobashi 2-2-1, Chuo-ku, Tokyo-To, 104-0031, Japan
Kojyokai Hirose Clinic, 2-14-7, Midori- cho, Tokorozawa-shi, Saitama, 359- 1111, Japan	Sugiura Clinic Institutional Review Board, Hon-cho 4-4-16-301, Kawaguchi-shi, Saitama-Ken, 332-0012, Japan
National Hospital Organization Yokohama Medical Center, 3-60-2, Harajuku, Totsuka-ku, Yokohama-city, Kanagawa, 245-8575, Japan*	National Hospital Organization CRB, Higashigaoka 2-5-21, Meguro-ku, Tokyo-To, 152-8621, Japan
Tohoku University Hospital, 1-1, Seiryō- machi, Aoba-ku, Sendai-city, Miyagi, 980-8574, Japan	Tohoku University Hospital Institutional Review board, Aoba-ku Seiryō-machi 1- 1, Sendai-shi, Miyagi-Ken, 980-8574, Japan
Showa University East Hospital, 2-14- 19, Nishinakanobu, Shinagawa-ku, Tokyo, 142-0054, Japan	Showa University Hospital Institutional Review Board, Hatanodai 1-5-8, Shinagawa-ku, Tokyo-To, 142-8666, Japan
Showa University Hospital, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142- 8666, Japan*	Showa University Hospital Institutional Review Board, Hatanodai 1-5-8, Shinagawa-ku, Tokyo-To, 142-8666, Japan
Nagasaki University Hospital, 1-7-1, Sakamoto, Nagasaki-city, Nagasaki, 852-8501, Japan*	Nagasaki University Hospital Institutional Review board, Sakamoto 1- 7-1, Nagasaki-shi, Nagasaki-Ken, 852-8501, Japan
Bay Side Misato Medical Center, 1617- 5, Niida, Kochi-shi, Kochi, 781-0112, Japan	IHL Shinagawa East One Medical Clinic Institutional Review Board, Konan 2-16- 1, Shinagawa East One Tower 3F, Minato-ku, Tokyo-To, 108-0075, Japan
Nagoya University Hospital, 65, Tsurumai-cho, Showa-ku, Nagoya-city, Aichi, 466-8560, Japan*	Nagoya University Hospital Institutional Review Board, Showa-ku Tsurumai-cho 65, Nagoya-shi, Aichi-Ken, 466-8560, Japan
Matsubara Mayflower Hospital, 944-25, Fujita, Kato-city, Hyogo, 673-1462, Japan	Matsubara Mayflower Hospital Institutional Review board, Fujita 944- 25, Kato-shi, Hyogo-Ken, 673-1462, Japan
Kagoshima Red Cross Hospital, 2545, Hirakawa-cho, Kagoshima-shi, Kagoshima, 891-0133, Japan	Kagoshima Red Cross Hospital Institutional Review Board, Hirakawa- cho 2545, Kagoshima-shi, 891-0133, Japan
Sagamihara National Hospital, 18-1, Sakuradai, Minami-ku, Sagamihara-shi, Kanagawa, 252-0392, Japan*	NHO CRB, Higashigaoka 2-5-21, Meguro-ku, Tokyo-To, 152-8621, Japan
Kita-Harima Medical Center, 926-250, Ichiba-cho, Ono-shi, Hyogo, 675-1392, Japan	Sanyakai Maebashi Hirosegawa Clinic Institutional Review Board, Chiyoda- machi 2-10-9, Maebashi-shi, Gunma- Ken, 371-0022, Japan
Iizuka Hospital, 3-83, Yoshio-machi, Iizuka-shi, Fukuoka, 820-8505, Japan*	Aso Co.,Ltd Iizuka Hospital Institutional Review Board, Yoshio-machi 3-83, Iizuka-shi, Fukuoka-Ken, 820-8505, Japan
University Hospital of Occupational and Environmental Health, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu-city, Fukuoka, 807-8555, Japan	Hospital of University of Occupational and Environmental Health Institutional Review Board, Yahatanishi-ku Iseigaoka 1-1, Kitakyushu-shi, Fukuoka-Ken, 807-8556, Japan

Description and address of research facility/hospital/institution	Name and address of IEC/IRB
Tobata General Hospital, 1-3-33, Fukuryugi, tobata-ku, Kitakyushu-shi, Fukuoka, 804-0025, Japan*	Nihonbashi Sakura Clinic Institutional Review Board, Nihombashikayaba-cho 1-9-2, Inamura Building 5F, Chuo-ku, Tokyo-To, 103-0025, Japan
St. Luke's International Hospital, 9-1, Akashi-cho, Chuo-ku, Tokyo, 104-8560, Japan	St. Luke's International Hospital Institutional Review Board, Akashi-cho 9-1, Chuo-ku, Tokyo-To, 104-8560, Japan
Kumamoto Orthopaedic Hospital, 1-15- 7, Kuhonji, Chuo-ku, Kumamoto-shi, Kumamoto, 862-0976, Japan*	Kumamoto Orthopaedic Hospital Institutional Review Board, Chuo-ku Shinyashiki 1-17-1, Kumamoto-shi, Kumamoto-Ken, 862-0975, Japan
Seiinkai Hokkaido Medical Center for Rheumatic Diseases, 3-1-45, Kotoni1jo, Nishi-ku, Sapporo-shi, Hokkaido, 063- 0811, Japan*	Seiinkai Hokkaido Medical Center for Rheumatic Diseases Institutional Review Board, Nishi-ku Kotoni 1jo 3-1- 45, Sapporo-shi, Hokkaido, 063-0811, Japan
Hakujuyikai Sasebo Chuo Hospital, -, 15, Yamato-cho, Sasebo-city, Nagasaki, 857-1195, Japan	Sasebo Chuo Hospital Institutional Review Board, Yamato-cho 15, Sasebo- shi, Nagasaki-Ken, 857-1195, Japan
Matsudo City General Hospital, 993-1, Sendabori, Matsudo-city, Chiba, 270- 2296, Japan	Matsudo City General Hospital Institutional Review Board, Sendabori 993-1, Matsudo-shi, Chiba-Ken, 270-2296, Japan
<b>Republic of Korea (N=5)</b>	
SoonChunHyang University Hospital Cheonan, 31, Suncheonhyang 6-gil, Dongnam-gu, Cheonan-si, 31151, Republic of Korea*	Institutional Review Board of SoonChunHyang University Hospital Cheonan, 31, Suncheonhyang 6-gil, Dongnam-gu, Cheonan-si, Chungcheongnam-do, 31151, Republic of Korea
The Catholic University of Korea Seoul St. Mary's Hospital, 222 Banpo-Daero, Seocho-gu, Seoul, 6591, Republic of Korea*	Institutional Review Board of The Catholic University of Korea, Seoul St. Mary's Hospital, 222 Banpo-Daero, Seocho-gu, Seoul, Gyeonggi-do, 06591, Republic of Korea
Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon- gil, Dongan-gu, Anyang-si, 431-070, Republic of Korea*	Institutional Review Board of Hallym University Sacred Heart Hospital, 22, Gwanpyeong-ro 170beon-gil, Dongan- gu, Anyang-si, Gyeonggi-do, 14068, Republic of Korea
Keimyung University Dongsan Hospital, 1035, Dalgubeol-daero, Dalseo-gu, Daegu-si, 42601, Republic of Korea*	Institutional Review Board of Keimyung University Dongsan Hospital, 56, Dalseong-ro, Jung-gu, clinical trial pharmacy, 3F, ByeolGwan, 41931, Republic of Korea
Asan Medical Center-Seoul-Korea-C, 88, Olympic-ro, 43-gil, Songpa-gu, Seoul, 5505, Republic of Korea	Institutional Review Board of Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Clinical Trial Pharmacy, 5th floor, West Building, Seoul, 05505, Republic of Korea
Seoul National University Hospital, 101 Daehak-ro Jongno-gu, Seoul, 3080, Republic of Korea	Institutional Review Board of Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
Inha University Hospital, 27, Inhang-ro, Jung-gu,, Incheon, 22332, Republic of Korea*	Institutional Review Board of Inha University Hospital, Jeongseok Bldg 366, Seohae-daero, Jung-gu, Incheon, 400-712, Republic of Korea
Severance Hospital, Yonsei University Health System, 50 Yonsei-ro Seodaemun-gu, Seoul, 120-752, Republic of Korea	Institutional Review Board of Severance Hospital, Yonsei University Health System, No. 31 Office, Pediatric Oncology Clinic, Yonsei Cancer Hospital, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea
Ajou University Hospital, 164, World Cup-ro, Yeongtong-gu, Suwon, 16499, Republic of Korea*	Institutional Review Board of Ajou University Hospital, 164, Worldcup-ro, Yeongtong-gu, Suwon, Gyeonggi-do, 16499, Republic of Korea
Kyung-Hee University Hospital at Gangdong, 892, Dongnam-ro, Gangdong-gu, Seoul, 134-	Institutional Review Board of Kyung Hee University Hospital at Gangdong, 892

Description and address of research facility/hospital/institution	Name and address of IEC/IRB
727, Republic of Korea*	Dongnam-ro Gangdong-gu, Seoul, 05278, Republic of Korea
Hanyang University Seoul Hospital, 222-1 Wangsimni-ro Seongdong-gu, Seoul, 4763, Republic of Korea*	Institutional Review Board of Hanyang University Seoul Hospital, 222-1, Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea
<b>Lithuania (N=6)</b>	
Siauliai Republican Hospital, Public Institution, V.Kudirkos g. 99, Siauliai, 76231, Lithuania	LIETUVOS BIOETIKOS KOMITETAS LITHUANIAN BIOETHICS COMMITTEE, Algirdo str.31, Vilnius, 3219, Lithuania
Klaipeda University Hospital, Liepojos g. 41, Klaipeda, LT-92288, Lithuania	LIETUVOS BIOETIKOS KOMITETAS LITHUANIAN BIOETHICS COMMITTEE, Algirdo str. 31, Vilnius, 3219, Lithuania
VAKK, JSC, Gaiziunu g. 3a, Kaunas, LT-50128, Lithuania*	LIETUVOS BIOETIKOS KOMITETAS LITHUANIAN BIOETHICS COMMITTEE, Algirdo str. 31, Vilnius, 3219, Lithuania
<b>Poland (N=108)</b>	
Centrum Kliniczno-Badawcze Lekarze Spolka Partnerska, ul. Studzienna 35- 36/A, Elblag, 82-300, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Reumed Zespol Poradni Specjalistycznych Filia nr 2, ul. Onyksowa 10, Lublin, 20-582, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Szpital Uniwersytecki nr 2 im. Dr Jana Biziele, Ujejskiego 75, Bydgoszcz, 85-168, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska Sp. Z o.o. Oddział w Gdyni, ul. Luzyczna 3c, Gdynia, 81-537, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska Sp. Z o.o., ul. Konckiego 3, Katowice, 40-040, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska sp. Z o.o. Oddział w Poznaniu, ul. Glogowska 31/33, Poznan, 60-702, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Nasz Lekarz Przychodnie Medyczne, ul. Stefana Batorego 18-22, Torun, 87-100, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska Sp. Z o.o. Oddział w Lodzi, ul. Składowa 35, Lodz, 90-127, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Amicare Sp. Z o.o. Sp.k, ul. Gen. Lucjana Zeligowskiego 46 lok. 10, Lodz, 90-644, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Centrum Medyczne Oporow, Solskiego 4A/1, Wroclaw, 52-416, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
ClinicMed Daniluk, Nowak Spolka Jawna, ul. Stoleczna 7 lok. 200, Bialystok, 15-879, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Centrum Badan Klinicznych S.C., ul.Sniadeckich 7/2, Poznan, 60-773, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Centrum Medyczne All-Med, ul. Henryka Sienkiewicza 23, Krakow, 30-033, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Rheuma Medicus Zaklad Opieki Zdrowotnej, ul.Pruszkowska 6, Warszawa, 02-118, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland



Description and address of research facility/hospital/institution	Name and address of IEC/IRB
Synexus Polska sp. Z o.o. Oddział we Wrocławiu, Ul. Marii. Curie- Skłodowskiej 12, Wrocław, 50-381, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Silmedica Sp. Z o. o., Gen. Władysława Sikorskiego 30 lok. 70, Katowice, 40-282, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
NBR Polska, 29 Listopada 18 A lok. 4, Warszawa, 00-465, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska Sp. Z o.o. Oddział w Częstochowie, Waly Generała Józefa Dwernickiego 43/45, Częstochowa, 42202, Poland*	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska SCM Sp. Z o.o. Gdansk, Beniewskiego 23, Gdansk, 80-382, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Centrum Medyczne Plejady, ul. Szafrana 5D/U2, U4, U5, Kraków, 30- 363, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Synexus Polska Sp. Z o.o., ul. Leszno 12, Warszawa, 01-192, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
RCMed, ul. Zeromskiego 41A, Sochaczew, 96-500, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
Medycyna Kliniczna, ul. Wronia 53 lok. B10 (Green Corner), Warszawa, 00- 874, Poland	KOMISJA BIOETYCZNA, ul. Nowowiejskiego 51, Poznań, 61-734, Poland
<b>South Africa (N=11)</b>	
University of Pretoria Clinical Research Unit, Room 2-54 Pathology Building, Dr Savage Road, Pretoria, 1, South Africa	University of Pretoria, Tswelopele Building opposite BMW building, Level 4, Room 4-59, Pretoria, Gauteng, 0002, South Africa
Synexus SA Stanza Clinical Research Centre, 2 Shilovhane Street,, Mamelodi East, 122, South Africa*	Pharma Ethics, 123 Amcor Road, Lyttelton Manor, Centurion, Pretoria, Gauteng, 0157, South Africa
Dr Halland & Louw Practice, Suite 136 Panorama Medical Centre, Cape Town, 7500, South Africa	Pharma Ethics, Suite 136 Panorama Medical Centre, Hennie Winterbach Avenue, Panorama, Cape Town, Western Cape, 7500, South Africa
Naidoo, A, Suite 509, Umhlanga Netcare Medical Centre, Durban, KwaZulu- Natal, 4319, South Africa*	Pharma Ethics, Umhlanga Netcare Medical Centre, Suite 509, 321 Umhlanga Rocks Drive, Umhlanga, Durban, KwaZulu-Natal, 4319, South Africa
Synexus SA Watermeyer Clinical Research Centre, Ground Floor Synexus Building, Pretoria, Gauteng, 184, South Africa	Pharma Ethics, 123 Amcor Road, Lyttelton Manor, Centurion, Pretoria, Gauteng, 0157, South Africa
Clinresco Centres (Pty) Ltd, Central Professional Suites, 1st floor, 20 Central Avenue, Kempton Park, 1619, South Africa	Pharma Ethics, Central Professional Suites, 1st floor, 20 Central Avenue, Kempton Park,
Arthritis Clinical Trial Centre, Room 201, The Park, Park road, Pinelands, Cape Town, 7405, South Africa*	Pharma Ethics, The Park, Suite 201, 2nd Floor, Park Road off Alexandra Road, Pinelands, Cape Town, Western Cape, 7405, South Africa
Winelands Medical Research Centre, 14A Oewer Park, Stellenbosch, 7600, South Africa*	Pharma Ethics, Suite G08 Winelands Mediclinic, C/o Saffraan and Rokewood Avenue, Die Boord, Stellenbosch, Western Cape, 7600, South Africa
<b>Spain (N=8)</b>	
Hospital Gregorio Marañón, C/ Dr. Esquerdo, 46, Madrid, 28007, Spain*	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital Clínico Universitario de Santiago, C/Paseo De La Chopana S/N, Santiago De	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de



Description and address of research facility/hospital/institution	Name and address of IEC/IRB
Compostela, 15706, Spain*	Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital Universitario Marqués de Valdecilla, Avda.de Valdecilla s/n, Santander, 39008, Spain	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Complejo Hospitalario Universitario de A Coruna, As Xubias 84, A Coruna, 15006, Spain	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital Universitario Reina Sofia, Avda Menendez Pidal S/N, Cordoba, 14004, Spain*	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital Germans Trias i Pujol, Ctra. Del Canyet, s/n, Badalona, 8916, Spain*	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital General Universitario de Elche, Cami, de la Almazara, 11, Elche, 03203, Spain	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital de Cruces, Pza Cruces s/n, Baracaldo, 48903, Spain*	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital Clínico Universitario de Valencia, Avda. Blasco Ibañez, 17, Valencia, 46010, Spain	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
Hospital Puerta de Hierro, C/ Manuel de Falla, 1, Majadahonda (Madrid), 28222, Spain*	Hospital General Universitario Gregorio Marañón, C/ Dr. Esquerdo 46, Pabellón de Gobierno, Primera Planta, Madrid, 28007, Spain
<b>United Kingdom (N=4)</b>	
MeDiNova East London Clinical Studies Centre, Blackburn House, 22 – 26 Eastern Road, Romford, Essex, RM1 3PJ, United Kingdom*	South Central – Berkshire B Research Ethics Committee, The Old Chapel Royal Standard Place, Nottingham, NG1 6FS, United Kingdom
MeDiNova Ltd, North London Clinical Studies Centre, Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex, HA6 2RN, United Kingdom	South Central – Berkshire B Research Ethics Committee, The Old Chapel Royal Standard Place, Nottingham, NG1 6FS, United Kingdom
Medinova Warwickshire Quality Research Site, 42 Station Rd, Kenilworth, Warwickshire, CV8 1JD, United Kingdom*	South Central – Berkshire B Research Ethics Committee, The Old Chapel Royal Standard Place, Nottingham, NG1 6FS, United Kingdom
Nuffield Orthopaedic Centre, Windmill Road, Oxford, OX3 7LD, United Kingdom**	Not Applicable
<b>United States (N=199)</b>	
Well Pharma Medical Research Corporation, Suite 100, 7000 Southwest 62 Avenue, South Miami, Florida, 33143, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
DM Clinical Research, 1307 FM 1960 Road West, Houston, Texas, 77065, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Arizona Arthritis and Rheumatology Research, 9520 W. Palm Ln. Suite 220, Phoenix, Arizona, 85037, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Oklahoma Medical Research Foundation, MS22, 825 N.E. 13th St, Oklahoma City, Oklahoma, 73104, United States	Oklahoma Medical Research Foundation Institutional Review Board, 825 North East 13th Street, MS 9, Oklahoma City, Oklahoma, 73104, United States

<b>Description and address of research facility/hospital/institution</b>	<b>Name and address of IEC/IRB</b>
Omega Research MetroWest, LLC, Suite 400, 1743 Park Center Drive, Orlando, Florida, 32835, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Precision Comprehensive Clinical Research Solutions, 5009 Heritage Ave, Colleyville, Texas, 76034, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Arizona Arthritis and Rheumatology Research, 4550 E Bell Rd, Phoenix, Arizona, 85032, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Advanced Rheumatology of Houston, Suite 120, 10857 Kuykendahl Road, The Woodlands, Texas, 77382, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Austin Regional Clinic, Suite 300, 6811 Austin Center Blvd., Austin, Texas, 78731, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Physicians Research Institute, Suite 120, 3901 Pine Lake Rd, Lincoln, Nebraska, 68516, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Pioneer Research Solutions, 21212 Northwest Fwy #375, Cypress, Texas, 77429, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Trinity Health, 400 Burdick Expressway East, Minot, North Dakota, 58701, United States	Trinity Hospital Institutional Review Board, One Burdick Expressway West, Minot, North Dakota, 58701, United States
Accurate Clinical Management – Partner, Suite 200, 11920 Astoria Boulevard, Houston, Texas, 77089, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Assuta Medical Group, Suite 1407, 2080 Century Park East, Los Angeles, California, 90067, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Metroplex Clinical Research Center, 8144 Walnut Hill Lane, Dallas, Texas, 75231, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Lakes Research LLC, 5801 NW 151 St., Miami Lakes, Florida, 33014, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States.
Arthritis & Osteoporosis Clinic, Suite 101, 611 W Hwy 6, Waco, Texas, 76710, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Stanford University, Suite 203, 1000 Welch Road, Palo Alto, California, 94304, United States*	Stanford University Administrative Panel on Human Subjects in Medical Research, 1501 South California Avenue, Mail Code: 5579, Palo Alto, California, 94304-5579, United States
East Bay Rheumatology Medical Group, 13851 East 14th Street, San Leandro, California, 94578, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Arthritis Clinic Of Central Texas, Building 2, Suite 2203, 1340 Wonder World Drive, San Marcos, Texas, 78666, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
La Salud Research Clinic, Suite 203, 8415 Southwest 24th Street, Miami, Florida, 33155, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Clinic of Robert A. Hozman, MD/CIS, 4709 Golf Road, Skokie, Illinois, 60076, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States

<b>Description and address of research facility/hospital/institution</b>	<b>Name and address of IEC/IRB</b>
Piedmont Arthritis Clinic, P.A., 3 St. Francis Drive, Greenville, South Carolina, 29601, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Medical Research Center of Miami II, Inc., Suite 209, 3971 SW 8TH Street, Miami, Florida, 33134, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Arthritis Consultants, Suite 240, 522 North New Ballas, St. Louis, Missouri, 63141, United States	Copernicus Group Institutional Review Board, 5000 Centre Green Way, Suite 200, Cary, North Carolina, 27513, United States
Great Lakes Clinical Trials, 5149 North Ashland Avenue, Chicago, Illinois, 60640, United States*	Copernicus Group Institutional Review Board, 5000 Centre Green Way, Suite 200, Cary, North Carolina, 27513, United States
Javed Rheumatology Associates INC, Suite 103, 550 Stanton Christiana Road, Newark, Delaware, 19713, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Bay Area Arthritis and Osteoporosis, 1355 Providence Road, Brandon, Florida, 33511, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
University of Florida, Jacksonville, Suite 220, 4555 Emerson Street, Jacksonville, Florida, 32207, United States	WIRB, 1019 39th Avenue South East, Suite 120, Puyallup, Washington, 98374, United States
Arizona Arthritis & Rheumatology Research, 2152 S Vineyard Ave Suite 129, Mesa, Arizona, 85210, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Medvin Clinical Research, 6673 Foothill Building, Tujunga, California, 91042, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Inland Rheumatology Clinical Trials, Inc., 1238 East Arrow Highway, Upland, California, 91786, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Chicago Clinical Research Institute, 611 West Roosevelt Road, Chicago, Illinois, 60607, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Arizona Arthritis and Rheumatology Research, 9520 W. Palm Ln. Suite 220, Phoenix, Arizona, 85037, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Cincinnati Rheumatic Disease Study Group, Inc. (CRDSG), 10495 Montgomery Road, Suite 26, Cincinnati, Ohio, 45242, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Piedmont Healthcare, Inc, Suite 500, 1800 Howell Mill Road, Atlanta, Georgia, 30318, United States	Western Institution Review Board, 1019 39th Avenue SE, Suite 120, Puyallup, Washington, 98374, United States
The Center for Rheumatology and Bone Research, Suite 306, 2730 University Blvd, West, Wheaton, Maryland, 20902, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
BayCare Medical Group Inc., 4612 N Habana Ave First Floor, Tampa, Florida, 33614, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Medvin Clinical Research, 500 W. San Bernardino Rd., Suite A, Covina, California, 91722, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Accurate Clinical Research, Inc., Suite A, 1610 West Baker Road, Baytown, Texas, 77521, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
NextGen Clinical Trials/South Texas Arthritis Care Center, 5414 Fredericksburg Rd Ste 150, San	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North

<b>Description and address of research facility/hospital/institution</b>	<b>Name and address of IEC/IRB</b>
Antonio, Texas, 78229, United States*	Carolina, 27513, United States
Arthritis & Osteoporosis Clinic of Brazos Valley, Suite 204, 1721 Birmingham Drive, College Station, Texas, 77845, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Rheumatology Clinic of Houston, P.A., Suite 240, 11307 FM 1960 West, Houston, Texas, 77065, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Dartmouth Hitchcock Medical Center, 1 Medical Center Drive, Lebanon, New Hampshire, 3756, United States	The Committee for the protection of Human Subjects at Dartmouth College, 63 S. Main Street, Dartmouth College, Hanover, New Hampshire, 03755-1404, United States
Rheumatology Center of San Diego, PC, Suite 220, 16516 Bernardo Center Dr., San Diego, California, 92128, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Innovation Medical Research Center, Inc, 9299 SW 152nd Street, Palmetto Bay, Florida, 33157, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Sun Valley Arthritis Center, LTD, 6818 W. Thunderbird Rd, Peoria, Arizona, 85381, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Lynn Health Science Institute, Suite 800, 3555 NW 58th Street, Oklahoma City, Oklahoma, 73112, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Centre for Rheumatology Immunology and Arthritis, 2900 West Cypress Creek Road, Fort Lauderdale, Florida, 33309, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Advent Health Medical Group, Suite 321, 13601 Bruce B Downs Boulevard, Tampa, Florida, 33613, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Allergy & Rheumatology Associates, LLC, 5100 Seminole Blvd, St. Petersburg, Florida, 33708, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Medvin Clinical Research, 12456 Washington Boulevard, Whittier, California, 90602, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Future Care Solution, LLC, 175 Fountainbleau Blvd, Miami, Florida, 33172, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Clinical Research Institute of Houston, Suite 200, 1140 Cypress Station Drive, Houston, Texas, 77090, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Better Health Clinical Research, Suite 100, 1665 Highway 34 East, Newnan, Georgia, 30265, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
West Texas Clinical Research, Suite 2C, 3809 22nd Street, Lubbock, Texas, 79410, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Mansfield Health Center, 200 Copeland Dr., Mansfield, Massachusetts, 2048, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Clinical Trials of Texas, Inc., 5430 Fredericksburg Road, San Antonio, Texas, 78229, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Allied Clinical Research, 6165 Ridgeview Court, Reno, Nevada, 89519, United States*	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States

Description and address of research facility/hospital/institution	Name and address of IEC/IRB
STAT Research, Suite 100B, 600 Aviator Court, Vandalia, Ohio, 45377, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States
Trinity Universal Research Associates, INC., 6300 Stonewood Dr, Plano, Texas, 75024, United States	Copernicus Group Institutional Review Board, 5000 Centregreen Way, Suite 200, Cary, North Carolina, 27513, United States

\*No patients enrolled; #Investigator signatory; investigator participated in the design of the clinical trial and the interpretation of the data; no patients enrolled. All centres participated in the trial under the US Investigational New Drug.

**Supplementary Table 2.** Permitted medications

Medications/Treatments	Restriction		
	Prior to study treatment period	During study treatment period (Day 1 to Week 24)	During 12-week follow-up
<b>Conventional synthetic DMARDs</b>			
<i>Patients must currently be taking at least one and at most two of the following concomitant csDMARDs</i>			
<p>Methotrexate 15-25mg/week oral or injected.</p> <p>A lower dose of <math>\geq 7.5</math> mg/week is acceptable if reduced for reasons of intolerance to MTX. e.g. hepatic or hematologic toxicity, or per local requirement (this must be clearly documented in medical records).</p> <p>Exception: A lower dose of 6 mg/week is only allowed if the minimum locally approved or recommended dose is lower than 7.5 mg/week.</p>	<p>At least one and at most two required (must have received at least 12 weeks treatment prior to Day 1, with stable and tolerated dose for at least 8 weeks prior to Day 1)</p>	<p>At least one and at most two required (dose must remain stable except adjustment for safety reasons)</p>	<p>Permitted</p>
Hydroxychloroquine up to 400 mg/day			
Chloroquine up to 250 mg/day			
Sulfasalazine up to 3000 mg/day			
Leflunomide up to 20 mg/day			
Tacrolimus up to 3 mg/day			
Bucillamine up to 100 mg/day (or up to 300 mg/day if permitted per local requirements)			
Iguratimod up to 50 mg/day			
<b>Corticosteroids</b>			
Stable dosing regimen of oral corticosteroids $\leq 10$ mg/day prednisolone or equivalent.	<p>Permitted</p>	<p>Permitted</p>	<p>Permitted</p>



	(dose must be stable 4 weeks prior to Day 1 and during screening if longer, with no changes except for safety reasons)	(dose must remain stable except for safety reasons)	
Intra-articular corticosteroids	Prohibited within 4 weeks prior to Day 1 and during screening, if longer.	A single IA injection Will be permitted between Week 12 and Week 20 only. The site of injection must be recorded.	Permitted
Inhaled steroids, topical steroids or topical immunosuppressive agents (e.g., eye drops, creams)	Permitted	Permitted	Permitted
<b>Analgesics</b>			
Acetaminophen (paracetamol) <b>taken as rescue for RA pain:</b> up to a maximum of 4g/day or locally approved maximum (if lower).	Permitted as needed (but not within 24 hours of Day 1 baseline visit)	Permitted as needed (but not within 24 hours of assessment visits)	Permitted
NSAIDs including aspirin and selective cyclooxygenase inhibitors.  <i>In this study, aspirin is considered a NSAID, except for low-doses (e.g. 75-150 mg/day) prescribed for cardiovascular or cerebrovascular disease.</i>	Permitted  <b>Patients on regular doses:</b> <u>Dosing regimen must be stable 7 days prior to Day 1</u> , no changes except for safety reasons. Do not discontinue	Permitted  <b>Patients on stable, regular doses:</b> From Day 1 to Week 12, dose regimen must not change except for safety reasons. Do not discontinue in advance of visits. After Week 12, any new	Permitted

Weak opioid analgesics (e.g. tramadol up to 400 mg/day, codeine)	in advance of visits.  <b>Patients on PRN prescription:</b> Record each dose during screening, or frequency with start/end dates, in CRF. Should not be taken within 24h of Day 1 baseline visit.	analgesic or change in regimen should not occur within 24h of assessment visits.  <b>Patients on PRN prescription:</b> Record each dose, or frequency with start/end dates, in CRF. Should not be taken within 24h of assessment visits.	
Strong opioid analgesics (e.g. morphine, hydromorphone, oxycodone, hydrocodone, fentanyl, meperidine, methadone)	Prohibited within 4 weeks prior to Day 1 and during screening, if longer.	Permitted after Week 12 After week 12, PRN or regular doses may be considered, but any new analgesic or change in regimen should not occur within 24h of assessment visits.  <b>Patients on PRN prescription:</b> Record each dose, or frequency with start/end dates, in CRF. Should not be taken within 24h of assessment visits.	Permitted
<b>Other Medications</b>			
Intra-articular Hyaluronic acid and any other intra-articular compounds used as lubricant in the joints.	Prohibited within 2 weeks prior to Day 1 and during screening, if longer.	Prohibited within 2 weeks prior to Week 12, Week 24 and Week 24 assessments.	Permitted

**Supplementary Table 3.** Prohibited medications/treatments

Medications/Treatments	Restriction		
	Prior to trial treatment period	During trial treatment period (Day 1 to Week 24)	During 12-week follow-up
<b>Treatments affecting GM-CSF pathway</b>			
Any treatment antagonising GM-CSF or its receptor	Prohibited (Exclusion criterion)	Prohibited (Except trial intervention)	Prohibited
<b>Conventional synthetic DMARDs</b>			
Combination treatment with MTX and leflunomide	Discontinue at least 12 weeks prior to Day 1	Prohibited	No restriction
Combination treatment of 3 or more csDMARDs	Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Hydroxychloroquine, chloroquine, sulfasalazine, minocycline, tacrolimus, cyclosporin, bucillamine, iguratimod If not being continued as background medication during the trial.	Discontinue at least 4 weeks prior to Day 1	Prohibited	No restriction
Leflunomide without washout treatment If not being continued as background medication during the trial.	Discontinue at least 12 weeks prior to Day 1	Prohibited	No restriction
Leflunomide with washout treatment for 11 days with oral cholestyramine (8 g three times daily) or charcoal (50 g four times daily) If not being continued as background medication during the trial.	Washout treatment must complete at least 2 weeks prior to Day 1	Prohibited	No restriction
<b>Biologic DMARDs</b>			
Anti-IL-6/IL-6R antagonist (including but not limited to sarilumab and tocilizumab).	Prohibited (Exclusion criterion)	Prohibited (Except trial intervention)	Prohibited
Etanercept (including its biosimilars).	Discontinue at least 4 weeks prior to Day 1	Prohibited	Prohibited

Any cell-depleting therapies, e.g. anti-CD20.	Discontinue at least 52 weeks prior to Day 1	Prohibited	Prohibited
Any other bDMARDs (experimental or approved).	Discontinue at least 8 weeks prior to Day 1	Prohibited	Prohibited
<b>Targeted synthetic DMARDs</b>			
JAK inhibitors (experimental or approved; e.g. tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib)	Discontinue at least 4 weeks or 5 half-lives (whichever is longer) prior to Day 1	Prohibited	Prohibited
Any other tsDMARD (experimental or approved)	Discontinue at least 4 weeks or 5 half-lives (whichever is longer) prior to Day 1	Prohibited	Prohibited
<b>Other RA therapies</b>			
Plasmapheresis or intravenous immunoglobulin (IVIG) or use of plasma filtering devices (e.g. Staph protein A column – Prosorba)	Discontinue at least 26 weeks prior to Day 1	Prohibited	Prohibited
<b>Corticosteroids</b>			
Irregular (not stable) doses or oral corticosteroids $\leq 10$ mg/day prednisolone or equivalent	Prohibited (except for safety reasons)	Prohibited (except for safety reasons)	No restriction
Oral corticosteroids $> 10$ mg/day prednisolone or equivalent	Discontinue/reduce to $\leq 10$ mg/day, at least 4 weeks prior to Day 1	Prohibited (except for safety reasons)	No restriction
Intra-muscular or intravenous corticosteroids	Discontinue at least 4 weeks prior to Day 1.	Prohibited (except for safety reasons)	No restriction
<b>Vaccine immunisations</b>			
Investigators should review and update the vaccination status of potential patients as per local guidelines for adult vaccination prior to entering them into the trial; refer to EULAR recommendations <sup>1</sup> where no local guidelines are available, with particular attention to the vaccination status of patients over 65 years of age. All patients who have not received the herpes zoster vaccine at trial entry will be recommended to complete vaccination $> 30$ days prior to			

randomisation. All patients may receive inactivated flu vaccines during the trial at the discretion of the investigator.			
Live-attenuated vaccinations	Discontinue at least 30 days prior to Day 1	Prohibited	Prohibited
BCG vaccination	Discontinue at least 365 days prior to Day 1	Prohibited	Prohibited

b/cs/tsDMARD, biologic/conventional synthetic/targeted synthetic disease-modifying anti-rheumatic drug; BCG, bacille Calmette–Guérin; CD20, cluster of differentiation; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IVIG, intravenous immunoglobulin; JAK, Janus kinase; RA, rheumatoid arthritis.

1. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79(1):39–52.



**Supplementary Table 4.** Major secondary endpoints at Week 24

	<b>Otilimab 90 mg QW N=156</b>	<b>Otilimab 150 mg QW N=158</b>	<b>Sarilumab 200 mg Q2W N=156</b>
<b>ACR20</b>			
Responders, % (SE)	58.1 (4.18)	60.5 (4.06)	65.1 (4.09)
Otilimab vs sarilumab, OR (95% CI)	0.75 (0.46, 1.23)	0.82 (0.50, 1.34)	
P value	0.2500	0.4362	
<b>HAQ-DI</b>			
LS mean change (SE)	−0.39 (0.050)	−0.45 (0.049)	−0.48 (0.050)
LS mean difference from sarilumab, (95% CI)	0.09 (−0.04, 0.23)	0.03 (−0.10, 0.16)	
P value	0.1845	0.6582	
<b>CDAI total score</b>			
LS mean change (SE)	−20.93 (1.040)	−20.75 (1.022)	−23.22 (1.048)
LS mean difference from sarilumab, (95% CI)	2.29 (−0.53, 5.11)	2.47 (−0.31, 5.26)	

P value	0.1112	0.0821	
<b>FACIT-Fatigue</b>			
LS mean change (SE)	6.55 (0.795)	7.21 (0.777)	7.99 (0.806)
LS mean difference from sarilumab, (95% CI)	-1.44 (-3.55, 0.68)	-0.78 (-2.88, 1.32)	
P value	0.1830	0.4681	
<b>Pain VAS</b>			
LS mean change (SE)	-25.06 (2.153)	-24.31 (2.115)	-30.62 (2.141)
LS mean difference from sarilumab, (95% CI)	5.56 (-0.23, 11.35)	6.31 (0.57, 12.05)	
P value	0.0597	0.0312 <sup>a</sup>	

<sup>a</sup>Step-down multiple testing procedure stopped at step 1, P value corresponds to higher reported efficacy of sarilumab versus otilimab.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; OR, odds ratio, QW, once weekly; Q2W, once every 2 weeks; SE, standard error; VAS, Visual Analogue Scale.

**Supplementary Table 5.** Additional secondary endpoints at Week 12

	<b>Placebo (N=79)</b>	<b>Otilimab 90 mg QW (N=156)</b>	<b>Otilimab 150 mg QW (N=158)</b>	<b>Sarilumab 200 mg Q2W (N=156)</b>
<b>CDAI LDA</b>				
Responders, % (SE)	14.2 (4.15)	20.7 (3.42)	18.2 (3.20)	28.1 (3.77)
Otilimab vs placebo, OR (95% CI)		1.83 (0.82, 4.09)	1.69 (0.74, 3.83)	3.03 (1.37, 6.67)
P value		0.1430	0.2106	0.0060 <sup>a</sup>
<b>CDAI remission</b>				
Responders, % (SE)	0.6 (1.30)	2.2 (1.25)	4.3 (1.70)	8.7 (2.38)
Otilimab vs placebo, OR (95% CI) <sup>b</sup>		-	-	-
P value		-	-	-
<b>DAS28-CRP</b>				
LS Mean change (SE)	-1.08 (0.139)	-1.34 (0.100)	-1.42 (0.098)	-2.15 (0.100)
LS mean difference from placebo, (95% CI)		-0.26 (-0.59, 0.07)	-0.34 (-0.67, - 0.02)	-1.07 (-1.41, -0.74)
P value		0.1176	0.0403 <sup>a</sup>	<0.0001 <sup>a</sup>
<b>DAS28-CRP ≤3.2</b>				
Responders, % (SE)	13.2 (4.06)	17.0 (3.19)	17.0 (3.14)	40.1 (4.16)
Otilimab vs placebo, OR (95% CI)		1.51 (0.64, 3.53)	1.66 (0.71, 3.88)	5.58 (2.48, 12.56)
P value		0.3449	0.2463	<0.0001 <sup>a</sup>
<b>DAS28-CRP &lt;2.6</b>				
Responders, % (SE)	1.8 (1.75)	10.2 (2.58)	7.2 (2.19)	22.2 (3.51)

Otilimab vs placebo, OR (95% CI)		7.95 (1.01, 62.49)	6.04 (0.74, 49.12)	22.01 (2.89, 167.75)
P value		0.0486 <sup>a</sup>	0.0928	0.0029 <sup>a</sup>
<b>ACR50</b>				
Responders, % (SE)	11.5 (3.79)	18.2 (3.28)	22.5 (3.47)	25.9 (3.74)
Otilimab vs placebo, OR (95% CI)		1.83 (0.77, 4.34)	2.39 (1.03, 5.55)	2.95 (1.27, 6.85)
P value		0.1688	0.0424 <sup>a</sup>	0.0116 <sup>a</sup>
<b>ACR70</b>				
Responders, % (SE)	6.1 (2.93)	5.9 (2.01)	10.8 (2.61)	13.3 (2.92)
Otilimab vs placebo, OR (95% CI)		1.02 (0.29, 3.55)	2.01 (0.64, 6.31)	2.65 (0.85, 8.24)
P value		0.9709	0.2340	0.0915
<b>Additional ACR Core Measures</b>				
<b>TJC68</b>				
LS Mean change (SE)	-9.19 (1.171)	-10.90 (0.832)	-11.61 (0.821)	-12.87 (0.838)
LS mean difference from placebo, (95% CI)		-1.71 (-4.47, 1.05)	-2.42 (-5.17, 0.34)	-3.68 (-6.46, -0.90)
P value		0.2256	0.0854	0.0095 <sup>a</sup>
<b>SJC66</b>				
LS Mean change (SE)	-6.96 (0.786)	-6.71 (0.558)	-7.73 (0.551)	-8.43 (0.562)
LS mean difference from placebo, (95% CI)		0.25 (-1.60, 2.10)	-0.77 (-2.62, 1.08)	-1.47 (-3.33, 0.40)
P value		0.7921	0.4136	0.1237
<b>PtGA</b>				
LS Mean change (SE)	-14.13 (2.723)	-17.00 (1.967)	-19.19 (1.932)	-24.05 (1.963)
LS mean difference from placebo, (95% CI)		-2.87 (-9.33, 3.59)	-5.06 (-11.49, 1.37)	-9.92 (-16.39, -3.45)
P value		0.3840	0.1230	0.0026 <sup>a</sup>

<b>PhGA</b>				
LS Mean change (SE)	–25.93 (2.681)	–34.21 (1.899)	–31.93 (1.889)	–35.43 (1.905)
LS mean difference from placebo, (95% CI)		–8.28 (–14.59, –1.97)	–5.99 (–12.30, 0.32)	–9.49 (–15.84, –3.14)
P value		0.0102 <sup>a</sup>	0.0627	0.0034 <sup>a</sup>
<b>CRP (mg/L)</b>				
LS Mean change (SE)	–0.15 (2.049)	–2.66 (1.449)	–4.54 (1.443)	–14.84 (1.473)
LS mean difference from placebo, (95% CI)		–2.52 (–7.34, 2.31)	–4.39 (–9.21, 0.42)	–14.70 (–19.57, –9.83)
P value		0.3071	0.0736	<0.0001 <sup>a</sup>
<b>Health-related quality of life</b>				
<b>SF-36 PCS</b>				
LS Mean change (SE)	3.72 (0.866)	5.08 (0.619)	5.03 (0.610)	5.61 (0.627)
LS mean difference from placebo, (95% CI)		1.36 (–0.67, 3.40)	1.31 (–0.71, 3.34)	1.89 (–0.15, 3.93)
P value		0.1898	0.2042	0.0698
<b>SF-36 MCS</b>				
LS Mean change (SE)	1.61 (1.024)	1.64 (0.731)	3.45 (0.720)	4.15 (0.744)
LS mean difference from placebo, (95% CI)		0.03 (–2.38, 2.43)	1.84 (–0.55, 4.23)	2.55 (0.13, 4.96)
P value		0.9818	0.1319	0.0389 <sup>a</sup>

<sup>a</sup>Statistical significance was not assessed within the step-down multiple testing procedure. <sup>b</sup>ORs and their 95% CIs were generated from the logistic regression model adjusted for baseline CDAI, treatment group and previously failed medication category. Model results were only reported if the maximum likelihood estimates existed and the convergence criterion was satisfied.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score-28 joints; LDA, low disease activity; LS, least squares; MCS, Mental Component



Summary; OR, odds ratio; PCS, Physical Component Summary; PhGA, physician's global assessment; PtGA, patient's global assessment; QW, once weekly; Q2W, once every 2 weeks; TJC, tender joint count; SE, standard error; SF-36, Short Form-36 questions; SJC, swollen joint count.

**Supplementary Table 6.** Additional secondary endpoints at Week 24

	<b>Otilimab 90 mg QW (N=156)</b>	<b>Otilimab 150 mg QW (N=158)</b>	<b>Sarilumab 200 mg Q2W (N=156)</b>
<b>CDAI LDA</b>			
Responders, % (SE)	31.2 (3.92)	30.1 (3.81)	42.6 (4.26)
Otilimab vs sarilumab, OR (95% CI)	0.57 (0.35, 0.95)	0.57 (0.35, 0.95)	
P value	0.0318 <sup>a</sup>	0.0295 <sup>a</sup>	
<b>CDAI remission</b>			
Responders, % (SE)	7.9 (2.33)	8.4 (2.32)	8.3 (2.39)
Otilimab vs sarilumab, OR (95% CI)	0.90 (0.37, 2.20)	1.03 (0.43, 2.43)	
P value	0.8192	0.9521	
<b>DAS28-CRP</b>			
LS Mean change (SE)	-1.67 (0.108)	-1.67 (0.106)	-2.38 (0.109)
LS mean difference from sarilumab, (95% CI)	0.71 (0.42, 1.00)	0.71 (0.42, 1.00)	
P value	<0.0001 <sup>a</sup>	<0.0001 <sup>a</sup>	
<b>DAS28-CRP ≤3.2</b>			
Responders, % (SE)	26.8 (3.75)	24.8 (3.60)	46.9 (4.28)
Otilimab vs sarilumab, OR (95% CI)	0.39 (0.23, 0.66)	0.37 (0.22, 0.62)	
P value	0.0004 <sup>a</sup>	0.0002 <sup>a</sup>	
<b>DAS28-CRP &lt;2.6</b>			
Responders, % (SE)	16.2 (3.14)	13.9 (2.88)	32.6 (4.03)
Otilimab vs sarilumab, OR (95% CI)	0.38 (0.21, 0.69)	0.34 (0.18, 0.61)	
P value	0.0014 <sup>a</sup>	0.0004 <sup>a</sup>	
<b>ACR50</b>			
Responders, % (SE)	23.6 (3.60)	30.1 (3.81)	42.9 (4.25)
Otilimab vs sarilumab, OR (95% CI)	0.40 (0.23, 0.67)	0.56 (0.34, 0.93)	
P value	0.0006 <sup>a</sup>	0.0245 <sup>a</sup>	

<b>ACR70</b>			
Responders, % (SE)	12.3 (2.81)	13.2 (2.83)	22.7 (3.63)
Otilimab vs sarilumab, OR (95% CI)	0.46 (0.23, 0.88)	0.50 (0.27, 0.95)	
P value	0.0202 <sup>a</sup>	0.0354 <sup>a</sup>	
<b>Additional ACR Core Measures</b>			
<b>TJC68</b>			
LS Mean change (SE)	-12.56 (0.876)	-12.81 (0.861)	-14.01 (0.875)
LS mean difference from sarilumab, (95% CI)	1.46 (0.90, 3.81)	1.21 (-1.13, 3.55)	
P value	0.2252	0.3118	
<b>SJC66</b>			
LS Mean change (SE)	-8.88 (0.569)	-9.17 (0.558)	-9.37 (0.569)
LS mean difference from sarilumab, (95% CI)	0.48 (-1.05, 2.01)	0.20 (-1.32, 1.72)	
P value	0.5357	0.7965	
<b>PtGA</b>			
LS Mean change (SE)	-22.45 (2.071)	-22.60 (2.035)	-29.19 (2.059)
LS mean difference from sarilumab, (95% CI)	6.74 (1.17, 12.30)	6.59 (1.07, 12.11)	
P value	0.0177 <sup>a</sup>	0.0194 <sup>a</sup>	
<b>PhGA</b>			
LS Mean change (SE)	-38.90 (1.856)	-37.22 (1.836)	-39.72 (1.861)
LS mean difference from sarilumab, (95% CI)	0.82 (-4.20, 5.84)	2.49 (-2.48, 7.47)	
P value	0.7500	0.3254	
<b>CRP (mg/L)</b>			
LS Mean change (SE)	-1.67 (0.108)	-1.67 (0.106)	-2.38 (0.109)
LS mean difference from sarilumab, (95% CI)	0.71 (0.42, 1.00)	0.71 (0.42, 1.00)	
P value	<0.0001 <sup>a</sup>	<0.0001 <sup>a</sup>	
<b>Health-related quality of life</b>			
<b>SF-36 PCS</b>			
LS Mean change (SE)	5.67 (0.707)	5.50 (0.694)	7.18 (0.710)
LS mean difference from sarilumab, (95% CI)	-1.51 (-3.39, 0.37)	-1.68 (-3.55, 0.18)	
P value	0.1148	0.0762	
<b>SF-36 MCS</b>			
LS Mean change (SE)	2.22 (0.772)	3.05 (0.756)	3.61 (0.780)
LS mean difference from sarilumab, (95% CI)	-1.39 (-3.44, 0.65)	-0.56 (-2.59, 1.47)	

P value	0.1817	0.5903	
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<sup>a</sup>Statistical significance was not assessed within the step-down multiple testing procedure. ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score-28 joints; LDA, low disease activity; LS, least squares; MCS, Mental Component Summary; OR, odds ratio, PCS, Physical Component Summary; PhGA, Physician Global Assessment; PtGA, Patient Global Assessment; QW, once weekly; Q2W, once every 2 weeks; SE, standard error; SF-36, Short Form-36 questions; SJC, swollen joint count; TJC, tender joint count.

**Supplementary Table 7.** Safety summary following switch from placebo to active treatment

Adverse event, n (%)	Placebo to otilimab 90 mg QW (N=24)	Placebo to otilimab 150 mg QW (N=25)	Placebo to sarilumab 200 mg Q2W (N=26)
<b>Week 12 to 24</b>			
Any AE	9 (38)	10 (40)	12 (46)
Any SAE	1 (4)	3 (12)	1 (4)
Any AESI	2 (8)	3 (12)	5 (19)
Serious infection*	1 (4)	0 (0)	1 (4)
Serious infection, excluding COVID-19*	1 (4)	0 (0)	0 (0)
Latent TB*	0 (0)	1 (4)	2 (8)
TB reactivation*	0 (0)	0 (0)	0 (0)
PAP*	0 (0)	0 (0)	0 (0)
COVID-19 diagnosis <sup>†</sup>	0 (0)	2 (8)	2 (8)
Any adjudicated CV event	0 (0)	0 (0)	0 (0)
Adjudicated MACE	0 (0)	0 (0)	0 (0)
VTE (DVT and/or PE)	0 (0)	0 (0)	0 (0)
DVT only	0 (0)	0 (0)	0 (0)
PE only	0 (0)	0 (0)	0 (0)
Any malignancy	0 (0)	0 (0)	0 (0)
Any malignancy, excluding NMSC	0 (0)	0 (0)	0 (0)
Fatal SAE	0 (0)	0 (0)	0 (0)

\*Only select AESIs with relevance to the MoA of otilimab or sarilumab are reported;

<sup>†</sup>Total cases (either AEs or SAEs).

AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CV, cardiovascular; DVT, deep vein thrombosis; MACE, major adverse cardiovascular event; MoA, mechanism of action; NMSC, non-melanoma skin cancer; PAP, pulmonary alveolar proteinosis; PE, pulmonary embolism; QW, once weekly; Q2W, once every 2 weeks; SAE, serious adverse event; TB, tuberculosis; VAS, Visual Analogue Scale; VTE, venous thromboembolism.

**Supplementary Table 8.** Most common ( $\geq 5\%$ ) AEs up to Week 12 and 24

Adverse event, n (%)	Pooled placebo (N=79)	Otilimab 90 mg QW (N=156)	Otilimab 150 mg QW (N=158)	Sarilumab 200 mg Q2W (N=156)
<b>Week 0 to 12</b>				
Any event	37 (47)	65 (42)	63 (40)	72 (46)
Injection-site reaction	0 (0)	8 (5)	6 (4)	14 (9)
RA	6 (8)	1 (<1)	3 (2)	2 (1)
Neutropenia	0 (0)	2 (1)	1 (<1)	8 (5)
<b>Week 0 to 24*</b>				
Any event		92 (59)	99 (63)	98 (63)
Injection-site reaction		9 (6)	10 (6)	17 (11)
Urinary tract infection		8 (5)	8 (5)	6 (4)
Alanine aminotransferase increased		2 (1)	6 (4)	11 (7)
COVID-19		8 (5)	6 (4)	4 (3)
Neutropenia		3 (2)	1 (<1)	13 (8)
Cough		5 (3)	10 (6)	1 (<1)

Events listed according to the MedDRA Preferred Terms used for the coding of events reported by investigators. \*Data reported for patients who were randomised to active treatments from baseline.

AE, adverse event; COVID-19, coronavirus disease 2019; QW, once weekly; Q2W, once every 2 weeks; RA, rheumatoid arthritis.



**Supplementary Table 9.** SAEs up to Week 12 and 24

Adverse event, n (%)	Pooled placebo (N=79)	Otilimab 90 mg QW (N=156)	Otilimab 150 mg QW (N=158)	Sarilumab 200 mg Q2W (N=156)
<b>Week 0 to 12</b>				
Any event	2 (3)	4 (3)	1 (<1)	5 (3)
Any blood and lymphatic system disorders	0	1 (<1)	0	2 (1)
Neutropenia	0	1 (<1)	0	2 (1)
Any infections and infestations	0	1 (<1)	0	1 (<1)
COVID-19 pneumonia	0	1 (<1)	0	1 (<1)
Any neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	1 (<1)	0	1 (<1)
Basal cell carcinoma	0	1 (<1)	0	0
Rectal cancer	0	0	0	1 (<1)
Any nervous system disorders	0	0	1 (<1)	1 (<1)
Optic neuritis	0	0	1 (<1)	0
Sciatica	0	0	0	1 (<1)
Any gastrointestinal disorders	1 (1)	0	0	0
Food poisoning	1 (1)	0	0	0
Any injury, poisoning and procedural complications	0	1 (<1)	0	0
Humerus fracture	0	1 (<1)	0	0
Any musculoskeletal disorders	1 (1)	0	0	0
Rheumatoid arthritis	1 (1)	0	0	0
<b>Week 0 to 24*</b>				
Any event		8 (5)	1 (<1)	12 (8)

Any infections and infestations		4 (3)	0	2 (1)
COVID-19 pneumonia		1 (<1)	0	2 (1)
COVID-19		1 (<1)	0	0
Liver abscess		1 (<1)	0	0
Osteomyelitis bacterial		1 (<1)	0	0
Sepsis		1 (<1)	0	0
Any blood and lymphatic system disorders		1 (<1)	0	2 (1)
Neutropenia		1 (<1)	0	2 (1)
Any cardiac disorders		0	0	2 (1)
Atrial fibrillation		0	0	2 (1)
Any injury, poisoning and procedural complications		2 (1)	0	0
Humerus fracture		1 (<1)	0	0
Post-procedural hypotension		1 (<1)	0	0
Any neoplasms benign, malignant, and unspecified (including cysts and polyps)		1 (<1)	0	1 (<1)
Basal cell carcinoma		1 (<1)	0	0
Rectal cancer		0	0	1 (<1)
Any nervous system disorders		0	1 (<1)	1 (<1)
Optic neuritis		0	1 (<1)	0
Sciatica		0	0	1 (<1)
Any congenital, familial, and genetic disorders		0	0	1 (<1)
Gilbert's syndrome		0	0	1 (<1)
Any gastrointestinal disorders		0	0	1 (<1)

Obstructive pancreatitis		0	0	1 (<1)
Any general disorders and administration site conditions		0	0	1 (<1)
Drowning		0	0	1 (<1)
Any investigations		0	0	1 (<1)
ALT increased		0	0	1 (<1)
AST increased		0	0	1 (<1)
Any vascular disorders		0	0	1 (<1)
Peripheral arterial occlusive disease		0	0	1 (<1)

Events listed according to the MedDRA Preferred Terms used for the coding of events reported by investigators. \*Data reported for patients who were randomised to active treatments from baseline.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; QW, once weekly; Q2W, once every 2 weeks; SAE, serious adverse event.

**Supplementary Table 10.** AESIs up to Week 12 and 24

Adverse event, n (%)	Pooled placebo (N=79)	Otilimab 90 mg QW (N=156)	Otilimab 150 mg QW (N=158)	Sarilumab 200 mg Q2W (N=156)
<b>Week 0 to 12</b>				
Any event	0 (0)	11 (7)	7 (4)	24 (15)
Serious infection	0 (0)	1 (<1)	0 (0)	1 (<1)
Serious infection, excluding COVID-19	0 (0)	0 (0)	0 (0)	0 (0)
Opportunistic infections	0 (0)	0 (0)	0 (0)	0 (0)
Active TB	0 (0)	0 (0)	0 (0)	0 (0)
Latent TB	0 (0)	0 (0)	0 (0)	0 (0)
TB reactivation	0 (0)	0 (0)	0 (0)	0 (0)
Neutropenia	0 (0)	2 (1)	1 (<1)	9 (6)
Persistent cough	0 (0)	0 (0)	0 (0)	0 (0)
Persistent dyspnoea	0 (0)	0 (0)	0 (0)	0 (0)
PAP	0 (0)	0 (0)	0 (0)	0 (0)
Serious hypersensitivity reactions	0 (0)	0 (0)	0 (0)	0 (0)
Injection-site reactions	0 (0)	8 (5)	6 (4)	14 (9)
<b>Week 0 to 24*</b>				
Any event		16 (10)	15 (9)	33 (21)
Serious infection		4 (3)	0 (0)	2 (1)
Serious infection, excluding COVID-19		2 (1)	0 (0)	0 (0)
Opportunistic infections		0 (0)	0 (0)	0 (0)
Active TB		0 (0)	0 (0)	0 (0)
Latent TB		0 (0)	4 (3)	2 (1)
TB reactivation		0 (0)	0 (0)	0 (0)

Neutropenia		3 (2)	1 (<1)	14 (9)
Persistent cough		0 (0)	0 (0)	0 (0)
Persistent dyspnoea		0 (0)	0 (0)	0 (0)
PAP		0 (0)	0 (0)	0 (0)
Serious hypersensitivity reactions		0 (0)	0 (0)	0 (0)
Injection-site reactions		9 (6)	10 (6)	17 (11)

Events listed according to the MedDRA Preferred Terms used for the coding of events reported by investigators. \*Data reported for patients who were randomised to active treatments from baseline.

COVID-19, coronavirus disease 2019; PAP, pulmonary alveolar proteinosis; QW, once weekly; Q2W, once every 2 weeks; TB, tuberculosis.

**Supplementary Table 11.** Summary of laboratory parameters worst grade shift from baseline grade over 24 weeks

	Maximum grade during time period														
	Otilimab 90 mg QW N=156					Otilimab 150 mg QW N=158					Sarilumab 200 mg Q2W N=156				
Baseline grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT increased	N=156					N=158					N=156				
Grade 0	125 (81%)	25 (16%)	4 (3%)	1 (<1%)	0	112 (72%)	37 (24%)	5 (3%)	2 (1%)	0	81 (53%)	68 (44%)	3 (2%)	1 (<1%)	0
Grade 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ALP increased	N=156					N=158					N=156				
Grade 0	137 (88%)	18 (12%)	0	0	0	136 (87%)	20 (13%)	0	0	0	145 (95%)	8 (5%)	0	0	0
Grade 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AST increased	N=156					N=158					N=156				
Grade 0	125 (81%)	28 (18%)	1 (<1%)	1 (<1%)	0	117 (75%)	35 (22%)	3 (2%)	1 (<1%)	0	104 (68%)	48 (31%)	1 (<1%)	0	0
Grade 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Blood bilirubin increased	N=156					N=158					N=156				
Grade 0	154 (>99%)	1 (<1%)	0	0	0	154 (99%)	1 (<1%)	0	0	0	140 (92%)	9 (6%)	2 (1%)	1 (<1%)	0
Grade 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0



	Maximum grade during time period														
	Otilimab 90 mg QW N=156					Otilimab 150 mg QW N=158					Sarilumab 200 mg Q2W N=156				
Baseline grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Total cholesterol (high)</b>	<b>N=156</b>					<b>N=158</b>					<b>N=156</b>				
Grade 0	58 (38%)	33 (22%)	0	0	0	66 (42%)	26 (17%)	0	0	0	33 (22%)	57 (38%)	0	0	0
Grade 1	4 (3%)	53 (35%)	4 (3%)	0	0	11 (7%)	48 (31%)	4 (3%)	0	0	1 (<1%)	52 (34%)	8 (5%)	0	0
Grade 2	0	0	0	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Haemoglobin decreased</b>	<b>N=156</b>					<b>N=158</b>					<b>N=156</b>				
Grade 0	84 (54%)	23 (15%)	7 (5%)	0	0	73 (47%)	38 (24%)	1 (<1%)	0	0	80 (52%)	15 (10%)	1 (<1%)	0	0
Grade 1	0	27 (17%)	5 (3%)	0	0	0	33 (21%)	6 (4%)	0	0	10 (7%)	31 (20%)	2 (1%)	0	0
Grade 2	0	0	3 (2%)	1 (<1%)	0	0	0	0	0	0	0	2 (1%)	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Haemoglobin increased</b>	<b>N=156</b>					<b>N=158</b>					<b>N=156</b>				
Grade 0	84 (54%)	1 (<1%)	0	0	0	73 (47%)	3 (2%)	0	0	0	80 (52%)	10 (7%)	0	0	0
Grade 1	3 (2%)	1 (<1%)	0	0	0	0	0	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	0	0
Grade 2	0	0	0	0	0	0	0	1 (<1%)	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Leukocytes decreased</b>	<b>N=156</b>					<b>N=158</b>					<b>N=156</b>				

	Maximum grade during time period														
	Otilimab 90 mg QW N=156					Otilimab 150 mg QW N=158					Sarilumab 200 mg Q2W N=156				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Baseline grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	140 (90%)	11 (7%)	2 (1%)	0	0	145 (93%)	8 (5%)	2 (1%)	0	0	99 (65%)	33 (22%)	17 (11%)	1 (<1%)	0
Grade 1	1 (<1%)	1 (<1%)	0	0	0	0	0	1 (<1%)	0	0	0	0	2 (1%)	1 (<1%)	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Neutrophil count decreased															
Grade 0	147 (95%)	1 (<1%)	4 (3%)	2 (1%)	1 (<1%)	145 (93%)	4 (3%)	4 (3%)	1 (<1%)	1 (<1%)	94 (61%)	14 (9%)	31 (20%)	8 (5%)	4 (3%)
Grade 1	0	0	0	0	0	0	0	1 (<1%)	0	0	0	0	0	2 (1%)	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Platelet count decreased															
Grade 0	151 (97%)	4 (3%)	0	0	0	153 (98%)	3 (2%)	0	0	0	142 (93%)	10 (7%)	1 (<1%)	0	0
Grade 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; QW, once weekly; Q2W, once every 2 weeks.