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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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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 ≥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.

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.

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 remission or low disease activity (LDA) with these treatment options.[1 2] It has been reported that the response to RA therapy generally decreases with each subsequent line of biologic (b) DMARD.[3] A 2018 observational study of over 13 000 patients with RA in Britain has estimated that 6% of patients are refractory to multiple bDMARDs[4]; therefore, many patients continue to have a substantial symptom burden despite treatment.[5] 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.[6] Patients are generally considered 'difficult-to-treat' if they have failed ≥2 bDMARDs/targeted synthetic (ts) DMARDs of different MoAs, after failing conventional synthetic (cs) DMARD therapy (unless contraindicated).[7] Furthermore, a number of patients who

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 ≥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.[8–10] Therefore, despite recent significant advances in RA therapy, there remains an unmet need for novel treatments in the management of RA.[7]

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.[11–13] 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.[13 14] 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.[15–17] 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.[13 15 16 18–20]

Otilimab is a high-affinity anti-GM-CSF monoclonal antibody that,[21] 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.[22] 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.[22] The weekly regimen was selected to overcome the apparent high clearance rate observed in BAROQUE.[22] 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 ≥18 years) with a clinical diagnosis of RA, per American College of Rheumatology (ACR)/EULAR 2010 Classification Criteria,[23] a global functional status in RA of class I, II or III per the ACR 1991 revised criteria,[24] a disease duration ≥6 months at screening, active disease at screening and baseline, defined by tender joint count (TJC) ≥6/68 and swollen joint count (SJC) ≥6/66 and a high-sensitivity C reactive protein measurement ≥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 ≥12 weeks prior to day 1. Patients must also have had an IR to an approved dose of ≥1 bDMARD (excluding anti-GM-CSF/GM-CSF receptor (R) and anti-IL-6/IL-6R therapies) and/or ≥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 ≥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

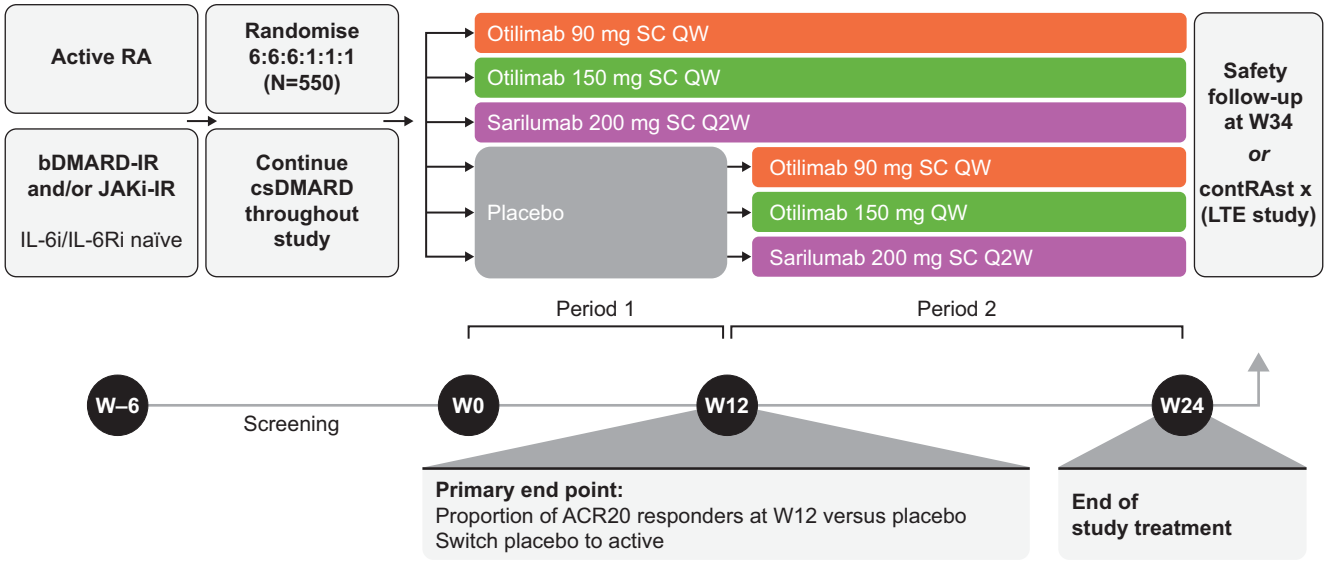

Figure 1 Trial design. ACR, American College of Rheumatology; b/csDMARD, biologic/conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin-6; IL-6Ri, IL-6 receptor inhibitor; IR, inadequate response; JAKi, Janus kinase inhibitor; LTE, long-term extension; Q2W, once every 2 weeks;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

bDMARD or ≥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 ≤10 mg/day prednisolone or equivalent was permitted throughout the trial. Analgesics, including acetaminophen (paracetamol) ≤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 ≥20% improvement in the ACR criteria (ACR20 response)[25] at week 12 for otilimab 90 mg and 150 mg veysus 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 (≤10) and remission (≤2.8), ACR20/50/70 response, Disease Activity Score (DAS)28-CRP ≤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 ≥1 dose of trial intervention. The safety population included all randomised patients who received ≥1 dose of trial treatment. The PK population included all patients in the safety population who had ≥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

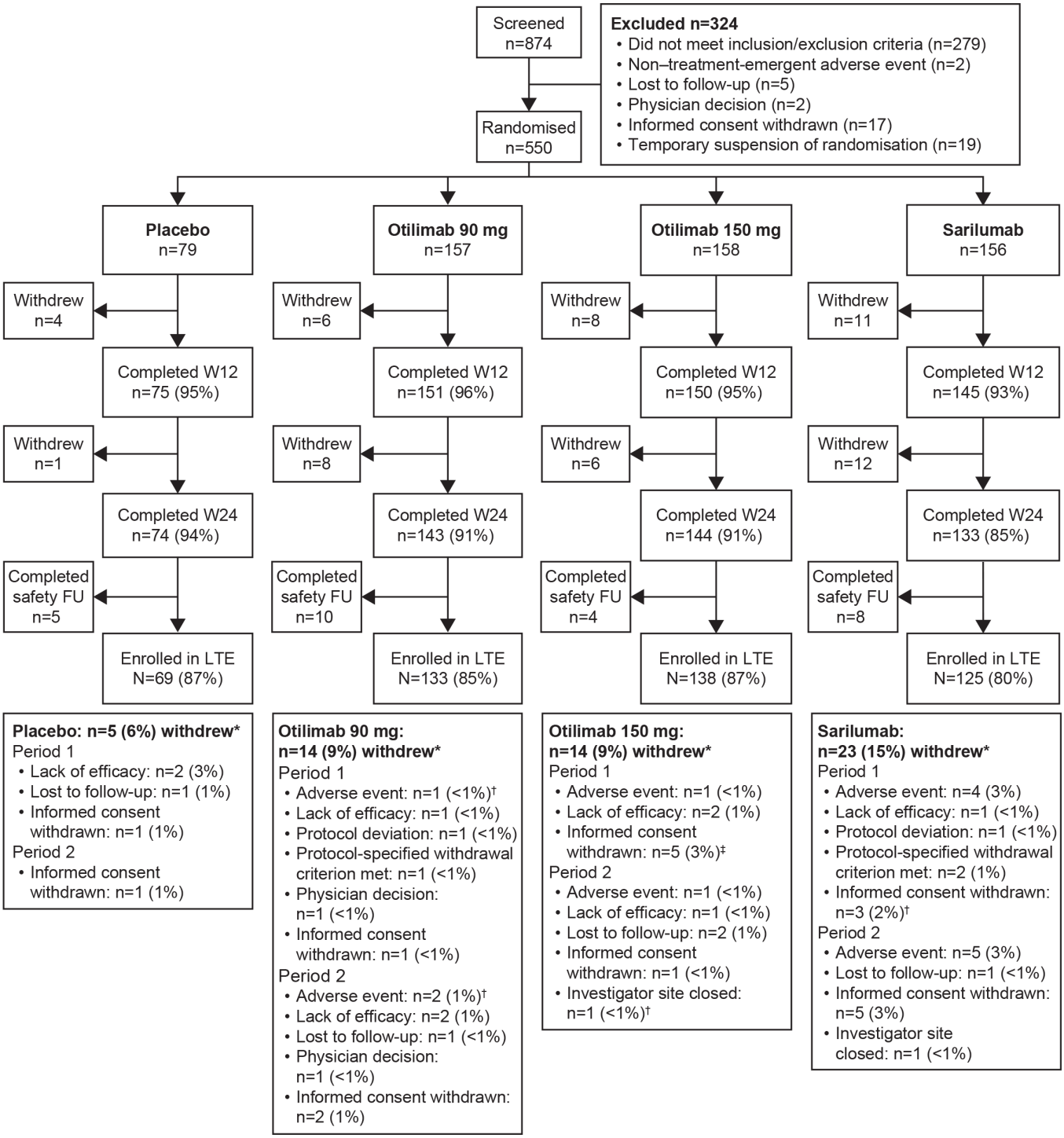

Figure 2 Patient disposition. *Only one primary reason for treatment discontinuation permitted. †Due to COVID-19 pandemic (n=1). ‡Only one patient in otilimab 90 mg and 150 mg groups and two patients in sarilumab group discontinued treatment due to COVID-19 pandemic. One patient randomised to otilimab 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)
Demographics					
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)
Baseline clinical characteristics					
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)
RA disease history					
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)
RA medications taken at baseline (day 1)					
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

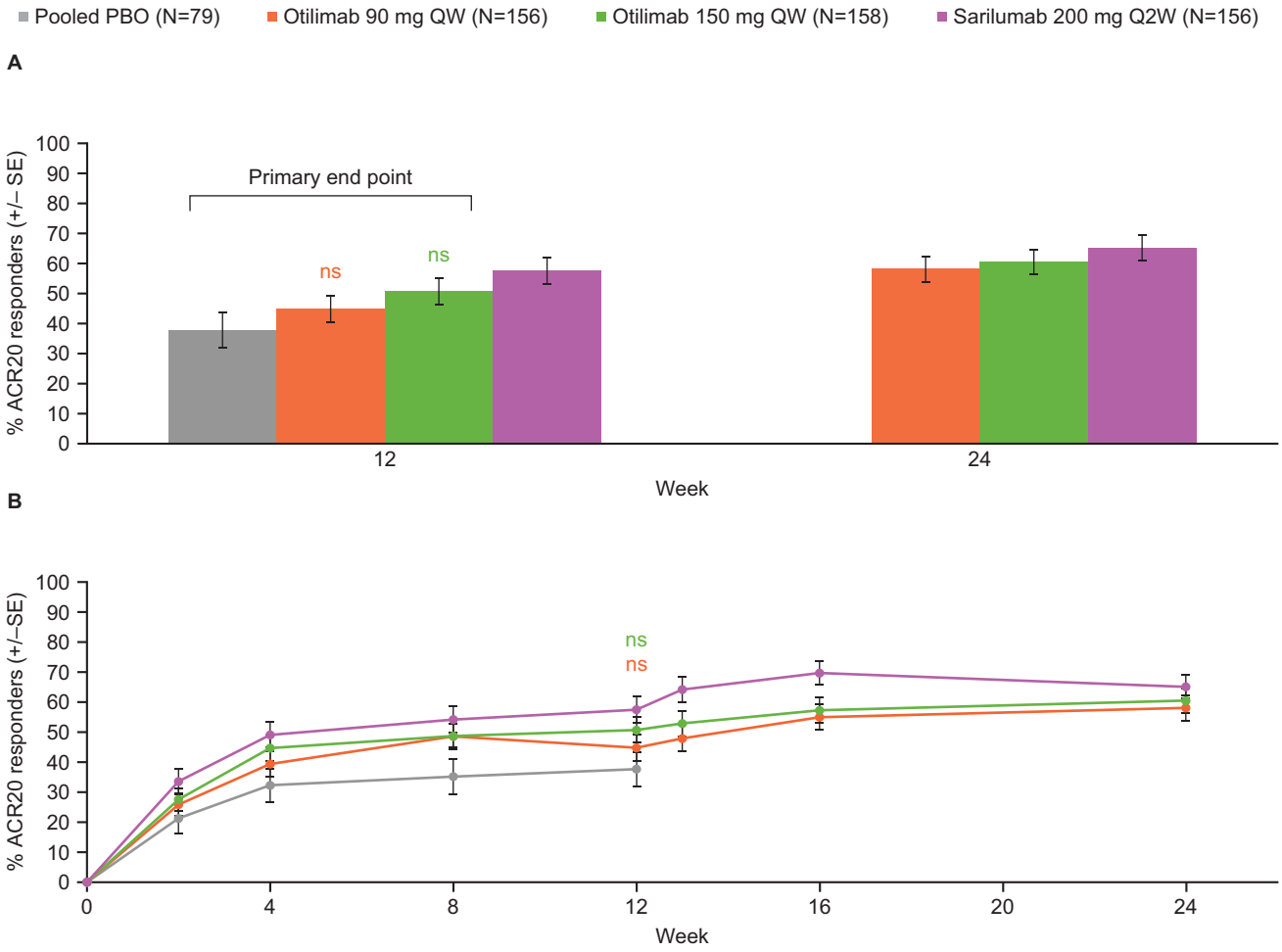

Figure 3 Proportion of patients achieving ACR20 at (A) weeks 12 and 24 and (B) each assessment visit. Statistical comparison of otilimab versus placebo. P values for all other comparisons are provided in the data tables. ACR, American College of Rheumatology; ns, not significant; PBO, placebo; Q2W, once 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 ≤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 ≤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 (≥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 ≤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 ≤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)
ACR20				
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*
HAQ-DI				
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*
CDAI				
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*
FACIT-Fatigue				
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
Pain VAS score				
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,[22] the percentage of ACR20 responders in the placebo group was notably higher than that observed in BAROQUE.[22] The reasons for the high placebo response are unknown. Similar to a study of atacicept,[26] 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[27–29] 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.[30] 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.[22] In contRAst 3, it was surprising that pain VAS scores were only marginally improved with either otilimab dose versus placebo, while

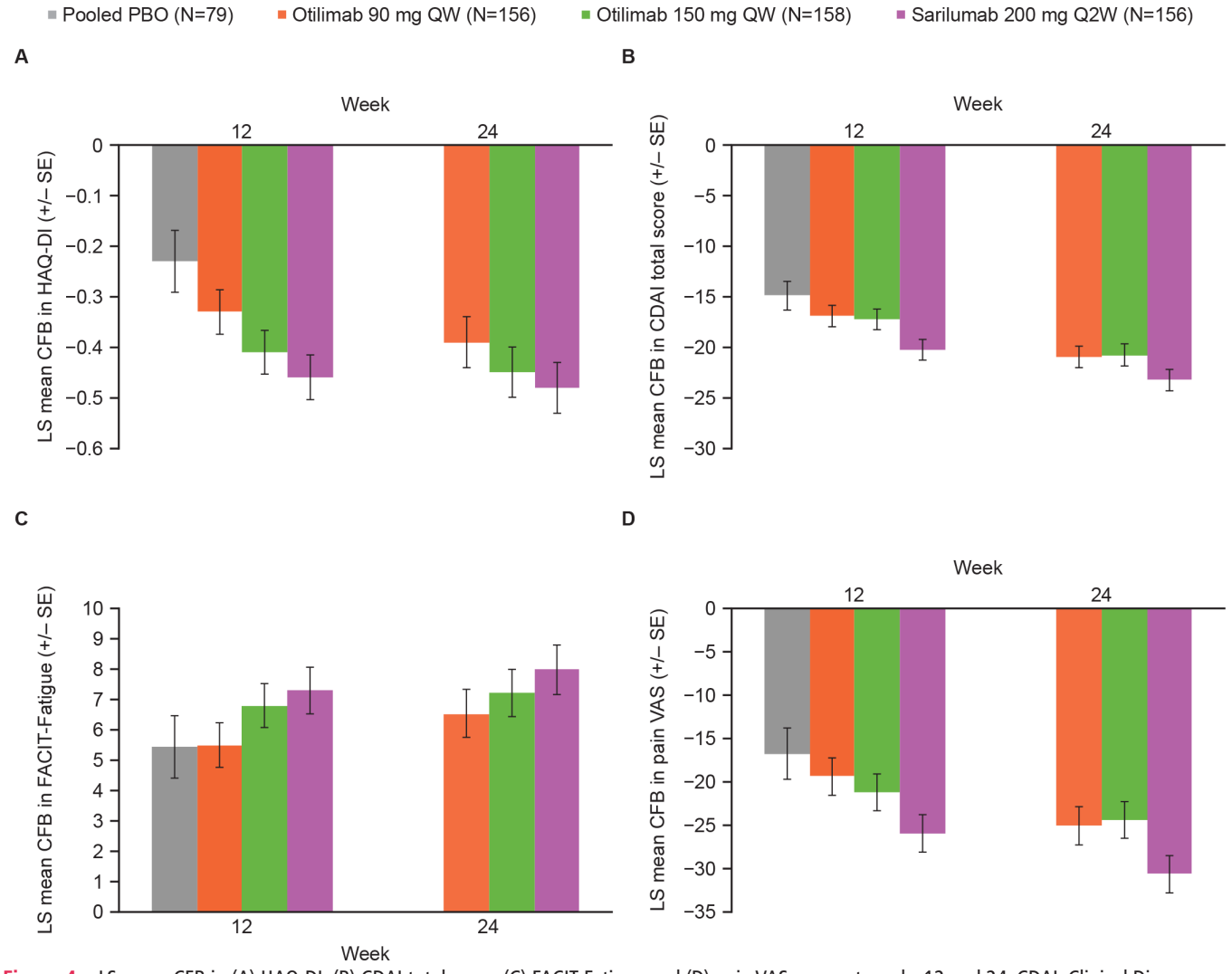

Figure 4 LS mean CFB in (A) HAQ-DI, (B) CDAI total score, (C) FACIT-Fatigue and (D) pain VAS score, at weeks 12 and 24. CDAI, Clinical Disease Activity Index; CFB, change from baseline; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; 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.[27–29] 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[31] 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.[32] 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.[22] Nevertheless, significant improvements in pain VAS were reported in BAROQUE despite non-significant CRP reductions,[22] 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,[33] 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,[28] but longer than the populations in previous anti-GM-CSF trials.[18 19 22] 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,[34] but do not support the use of otilimab in this patient population. As both GM-CSF and IL-6 signal via the JAK pathway,[35] 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)
Weeks 0–12				
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)
Weeks 0–24‡				
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,[36–38] 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.[39 40] Similarly, there were concerns of impairment of immunological responses, leading to TB reactivation.[41 42] 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.[22 33] 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.[18 19 22 43 44]

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.[18 27 28] 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[45–47] 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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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.

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