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CLINICAL SCIENCE

Olokizumab, a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study

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ABSTRACT

Objective To evaluate the efficacy and safety of olokizumab (OKZ) in patients with active rheumatoid arthritis despite treatment with methotrexate (MTX).

Methods In this 24-week multicentre, placebo-controlled, double-blind study, patients were randomised 1:1:1 to receive subcutaneously administered OKZ 64 mg once every 2 weeks, OKZ 64 mg once every 4 weeks, or placebo plus MTX. The primary efficacy endpoint was the proportion of patients achieving an American College of Rheumatology 20% (ACR20) response at week 12. The secondary efficacy endpoints included percentage of subjects achieving Disease Activity Score 28-joint count based on C reactive protein <3.2, Health Assessment Questionnaire Disability Index at week 12, ACR50 response and Clinical Disease Activity Index ≤2.8 at week 24. Safety and immunogenicity were assessed throughout the study.

Results A total of 428 patients were randomised. ACR20 responses were more frequent with OKZ every 2 weeks (63.6%) and OKZ every 4 weeks (70.4%) than placebo (25.9%) (p<0.0001 for both comparisons). There were significant differences in all secondary efficacy endpoints between OKZ-treated arms and placebo. Treatment-emergent serious adverse events (TESAEs) were reported by more patients in the OKZ groups compared with placebo. Infections were the most common TESAEs. No subjects developed neutralising antidrug antibodies.

Conclusions Treatment with OKZ was associated with significant improvement in signs, symptoms and physical function of rheumatoid arthritis without discernible differences between the two regimens. Safety was as expected for this class of agents. Low immunogenicity was observed.

Trial registration number NCT02760368.

Key messages

What is already known about this subject?

- Olokizumab (OKZ) is a new humanised monoclonal antibody targeting interleukin 6 ligand.
- Two placebo-controlled randomised phase II trials of OKZ in rheumatoid arthritis (RA) showed that it was significantly better than placebo across a range of doses; however, these studies were conducted in patients who had previously failed antitumour necrosis factor therapy and were of 12 weeks' duration.
- Long-term extension studies of these two controlled trials were conducted, but they were open-label and uncontrolled and all patients received the same dose of OKZ, 120 mg given every 2 weeks.

What does this study add?

- This study is the first of three phase III randomised controlled trials of OKZ in RA.
- In contrast to the phase II studies that were conducted in patients who had failed anti-TNF therapy, the current study was performed in patients who had an inadequate response to methotrexate.
- This phase III study was of 6 months' duration and tested two regimens of OKZ versus placebo and met all primary and ranked secondary efficacy endpoints.
- This study provides important information on the efficacy, safety and quality of life effects of OKZ that were not previously known.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that if left inadequately treated can lead to significant disability, morbidity and mortality.[1–3] Current guidelines recommend a treat to target strategy in order to attain acceptable level of disease control and prevent long-term disability.[1 3] A number of effective therapies with different modes of action are currently available for RA; however, many patients with active RA fail to achieve defined targets of therapy, namely low disease activity or remission.[1 3 4]

The proinflammatory cytokine interleukin 6 (IL-6) plays a significant role in the pathogenesis of RA and two anti-IL-6 receptor (IL-6R) antibodies have been shown to be relatively safe and effective and are approved for treatment of RA.[5–9]

Key messages

How might this impact on clinical practice or future developments?

- The current phase III study of OKZ will be part of future registration of this agent in various countries.
- OKZ was already approved for use in the Russian Federation.
- The data provided in the study will be very important for clinicians who might want to use this agent in their practice once it is approved since it provides meaningful controlled data on the efficacy and safety of this agent in a population of patients with inadequate response to methotrexate.

Olokizumab (OKZ) is an anti-IL-6 monoclonal antibody that binds directly to IL-6 at a specific site and neutralises its activity through blocking hexamer formation of the extracellular signalling complex inhibiting transmembrane signalling.[10] In early clinical studies it was shown that OKZ resulted in a rapid reduction in the level of IL-6 and C reactive protein (CRP) that lasted over an extended period of time due to OKZ's long half-life of approximately 31 days.[11]

OKZ in doses ranging from 60 mg to 240 mg administered every 2 weeks or every 4 weeks was relatively safe and effective in reducing signs and symptoms of RA in two phase II randomised controlled trials in patients with RA who had failed to respond to antitumour necrosis factor (anti-TNF) therapy.[12 13] Based on findings from these two studies, as well as information from earlier studies, two doses of OKZ, 64 mg every 2 weeks and 64 mg every 4 weeks, were selected for advancement to phase III.[11] The lowest two doses tested in phase II were chosen to achieve efficacy while minimising potential adverse effects. Here we report the full results of the first completed phase III study of OKZ in patients with active RA despite treatment with methotrexate (MTX).

METHODS

Study design

This phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trial was conducted at 42 hospitals in Russia, Belarus and Bulgaria from May 2016 to April 2019. Written informed consent was obtained from each patient.

After week 24, patients had the choice of either enrolling into an ongoing open-label study or entering the safety follow-up period.

Patient inclusion and exclusion criteria

Adults were eligible for inclusion if they had active RA (swollen joint count ≥6 (66-joint count), tender joint count ≥6 (68-joint count) and CRP >6 mg/L) classified by the American College of Rheumatology/European League Against Rheumatism 2010 revised classification criteria[14] for at least 12 weeks prior to screening and had an inadequate response to treatment with MTX for at least 12 weeks at a dose of 15–25 mg/week (or ≥10 mg/week if intolerant to higher doses). The dose and route of administration of MTX must have been stable for at least 6 weeks.

Exclusion criteria were other inflammatory or rheumatic diseases and Steinbrocker class IV functional capacity. Also excluded were those who had a prior exposure to IL-6 or IL-6R inhibitors, Janus kinase inhibitors, those treated with cell-depleting agents or those concurrently on disease-modifying antirheumatic drugs (DMARDs) other than MTX. Prior use of biologic DMARDs was an exclusion criterion with the exception of subjects who discontinued anti-TNF therapy due to reasons other than lack of efficacy. Non-steroidal anti-inflammatory drugs and glucocorticoids in doses less than or equal to 10 mg/day prednisone or equivalent were allowed if their doses were stable during the 2 weeks prior to study enrolment. Patients with a history of malignancies within the last 5 years (successfully treated carcinoma of the cervix in situ, basal cell carcinoma and squamous cell carcinoma of the skin were allowed if beyond 1 year prior to screening), recurrent infections, primary or secondary immunodeficiency, hepatitis B or C, active tuberculosis (TB) or other uncontrolled medical conditions, or prespecified abnormal laboratory values were excluded. Patients with latent TB infection were allowed to participate if they had started appropriate anti-TB therapy at least 30 days prior to randomisation (see online supplemental material for additional selection criteria).

Randomisation and blinding

Patients were randomised 1:1:1 to receive subcutaneous injections of OKZ 64 mg every 2 weeks, OKZ 64 mg once every 4 weeks, or placebo (PBO) for 24 weeks with continuation of their background MTX using an automated randomisation system. Subjects who discontinued the randomised treatment earlier were required to continue the study without study treatment administration; patients could discontinue study treatment but completed the study.

All patients, investigators, clinical site staff, contract research organisation's staff and the sponsor's staff directly involved in the study were blinded. Joint assessments were performed by independent assessors, blinded to study drug assignment and all other study assessments (see online supplemental material for additional details).

Rescue medication

Starting at week 14, non-responders, defined as subjects in any treatment group who did not improve by at least 20% in both swollen and tender joint counts (66–68 joints), were prescribed rescue medication (sulfasalazine and/or hydroxychloroquine) in addition to their study treatment (see online supplemental material for details of the prior and concomitant medications).

Endpoints

The primary endpoint was the proportion of patients achieving the American College of Rheumatology 20% (ACR20) response at week 12.

Ranked secondary endpoints were percentage of subjects achieving Disease Activity Score 28 based on C reactive protein (DAS28-CRP) <3.2 at week 12, improvement in physical ability from baseline to week 12 measured by the Health Assessment Questionnaire Disability Index (HAQ-DI), ACR50 response at week 24 and percentage of subjects with Clinical Disease Activity Index (CDAI) ≤2.8 (remission) at week 24.

Quality of life was assessed using several questionnaires including Short Form-36 (SF-36) Physical Component Summary (PCS), Mental Component Summary (MCS) and total scores, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F).

Standard safety monitoring, including assessment of adverse events, serious adverse events and laboratory tests via the central laboratory, was performed regularly.

Determination of antidrug antibodies (ADA) in plasma samples was done using electrochemiluminescence assay (Covance

Laboratories, Harrogate, North Yorkshire, UK). For detection of neutralising ADAs, a cell-based assay was used (Eurofins BioPharma Product Testing Munich, Planegg/Munich, Germany).

An independent external Data and Safety Monitoring Board reviewed the safety data throughout the study. Major adverse cardiovascular events (MACE) were adjudicated by a Cardiovascular Adjudicated Committee and were defined as cardiovascular death or death from undetermined cause, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, hospitalisation for unstable angina requiring unplanned revascularisation and coronary revascularisation procedures.

Statistical analyses

The ACR20 response at week 12 for each of the active treatment groups was compared with PBO using a 2×2 χ^2 test for equality of proportions. To control the overall type I error rate at a one-sided $\alpha=0.025$, Bonferroni adjustment was used for the tests related to each of the OKZ dose regimens versus PBO (ie, one-sided $\alpha=0.0125$ for each dose). A gate-keeping strategy with a fixed order of hypothesis was used for the primary and secondary endpoints within each OKZ dose regimen independently (figure 1).

To detect a difference between at least one OKZ dose regimen and PBO, a sample size of 420 patients randomised in a 1:1:1 ratio was estimated to ensure sufficient disjunctive power (100% for testing the primary hypothesis (ACR20 at week 12) and 98% for the secondary endpoint of DAS28-CRP <3.2 rate at week 12).

The secondary endpoints that were binary in nature were analysed as per the primary endpoint. For analyses of binary variables, inability to remain on randomised treatment through the time point of interest was defined as non-response with

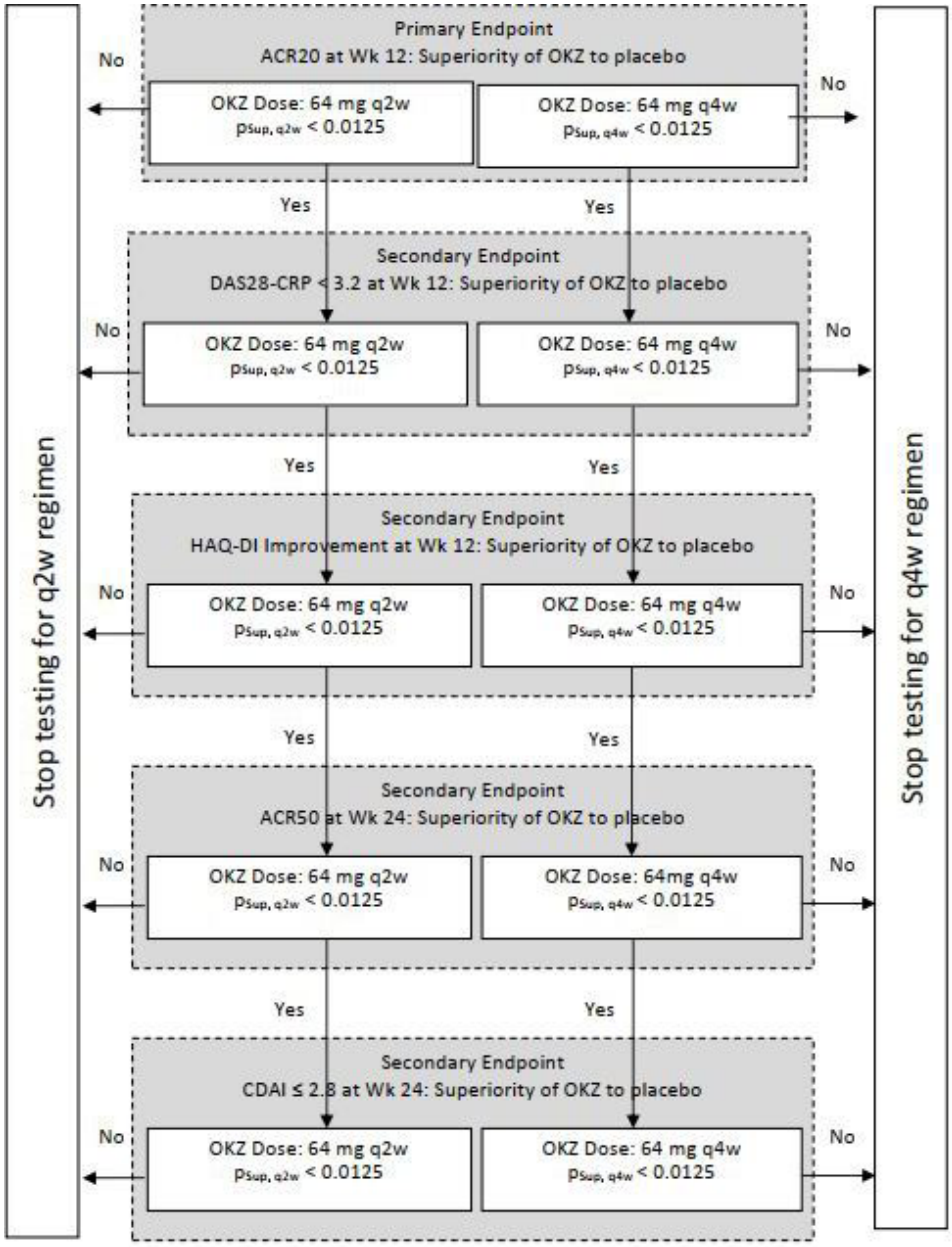

Figure 1 Gate-keeping strategy. $p_{Sup,\ q2w}$ and $p_{Sup,\ q4w}$ represent p values from a one-sided test of superiority versus placebo for OKZ dose regimens 64 mg q2w and q4w. ACR, American College of Rheumatology response; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28 based on C reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; OKZ, olokizumab; q2w, every 2 weeks; q4w, every 4 weeks; Wk, week.

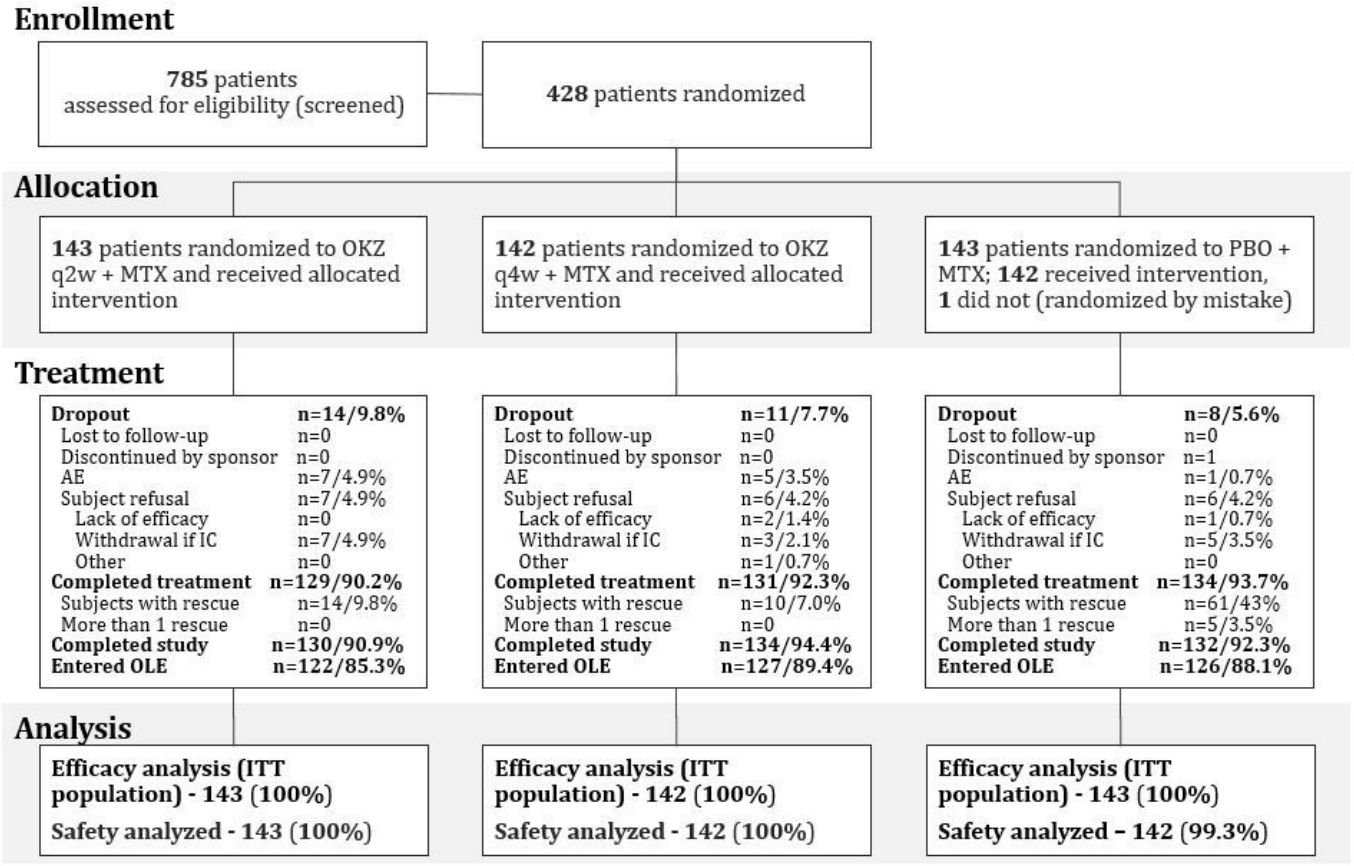

Figure 2 Patient disposition. AE, adverse event; IC, informed consent; ITT, intention-to-treat; MTX,methotrexate; OKZ, olokizumab; OLE, open-label extension; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks.

respect to the corresponding endpoint. For analyses of binary variables, in case of missing visits or assessments not performed for reasons other than treatment or study discontinuation intermediate missing data were imputed using surrounding visits.

Efficacy endpoints that were continuous in nature were analysed using an analysis of covariance model adjusted for the baseline value of the corresponding parameter. For analyses of continuous endpoints, subjects who discontinued randomised treatment prematurely but remained in the study through the time point of interest were included using all collected measurements, including those from assessments post treatment discontinuation. In case of missing values, return to baseline values was assumed and was implemented using multiple imputation accounting for the uncertainty of missing data according to the methodology of Rubin.[15]

The primary analysis was performed for intention-to-treat population, defined as all randomised patients. The safety population included all subjects who received at least one dose of the study treatment.

Protocol-specified statistical analyses were performed using Statistical Analysis System V.9.4 or higher.

RESULTS

Disposition

A total of 428 patients were randomised to OKZ 64 mg every 2 weeks (n=143), OKZ 64 mg every 4 weeks (n=142) or PBO (n=143). One patient failed screening, was randomised in error to the PBO group and was withdrawn once the error was discovered, before receiving study treatment; the safety population consisted of 427 subjects (figure 2). The three treatment groups were well balanced for baseline demographic and disease characteristics (table 1).

A total of 92.1% (n=394) of subjects completed the treatment period: 92.3% (n=131) in OKZ every 4 weeks, 90.2% (n=129) in OKZ every 2 weeks and 93.7% (n=134) in the PBO group. The most common reasons for treatment discontinuation were withdrawal of informed consent and adverse events (figure 2).

A higher proportion of patients in the PBO group (43%) received rescue medication(s) compared with patients on OKZ every 4 weeks (7%) or OKZ every 2 weeks (9.8%).

At week 24 of the study, 122 (85.3%) patients on OKZ every 2 weeks, 127 (89.4%) on OKZ every 4 weeks and 126 (88.1%) on PBO were enrolled in the open-label extension study .

Efficacy

The primary efficacy endpoint, ACR20 response rate at week 12, was 70.4% in OKZ every 4 weeks and 63.6% in OKZ every 2 weeks, both significantly greater than 25.9% in the PBO group ($p<0.0001$ for both comparisons) (table 2). Separation of the ACR20 response in the OKZ treatment groups from PBO was seen starting around week 2 and plateauing at week 12 (figure 3).

The secondary endpoint of DAS28-CRP <3.2 at week 12 was achieved by 33.6% and 38.7% of patients on OKZ every 2 weeks and every 4 weeks, respectively, significantly higher than those in the PBO group (3.5%, $p<0.0001$ for both comparisons) (table 2, figure 3).

Significant improvements in physical function as assessed with HAQ-DI were observed at week 12 for subjects in both OKZ dosage groups compared with PBO. HAQ-DI improvements from baseline (least squares mean change) were 0.56, 0.54 and

Table 1 Demographic and other baseline characteristics (ITT population)*

Characteristics, mean (SD) unless otherwise specified	OKZ every 2 weeks N=143	OKZ every 4 weeks N=142	PBO N=143
Age (years)	52.0 (11.8)	49.1 (12.1)	52.7 (11.3)
Female (%)	81.1	83.1	83.9
Duration of RA (years)	8.7 (8.0)	7.3 (7.0)	8.4 (7.8)
MTX dose (mg)†	16.1 (3.4)	16.3 (3.4)	16.1 (3.7)
Duration of prior MTX use (weeks)	201.5 (232.1)	157.4 (165.6)	210.1 (208.2)
Glucocorticoid use, n (%)	52 (36.4)‡	50 (35.2)‡	41 (28.7)‡
Prednisone dose or equivalent (mg)	7.6 (6.0)	6.1 (2.3)	6.6 (2.4)
Prior exposure to TNF inhibitors, n (%)	0	0	4 (2.8)
BMI (kg/m^2)	26.6 (5.1)	26.4 (5.5)	26.9 (5.0)
RF+ (≥15 IU/mL), n (%)	115 (80.4)	122 (85.9)	127 (88.8)
Anti-CCP+ (>10 IU/mL), n (%)	110 (76.9)	115 (81.0)	117 (81.8)
CRP (mg/L)§	23.5 (23.1)	22.7 (22.7)	25.8 (28.7)
TJC¶	24.4 (11.4)	22.2 (10.3)	24.0 (11.3)
SJC¶	14.8 (6.5)	14.5 (6.7)	14.6 (6.9)
DAS28-CRP	6.0 (0.7)	5.9 (0.7)	6.0 (0.8)
CDAI score (0–76)	40.5 (9.8)	38.7 (9.4)	40.4 (10.5)
HAQ-DI score	1.74 (0.47)	1.64 (0.50)	1.78 (0.49)
PtGA (VAS) (mm)	70.4 (16.0)	68.5 (14.5)	69.6 (15.9)
Pain (VAS) (mm)	70.2 (16.3)	67.4 (18.5)	68.3 (17.6)
PGA (VAS) (mm)	70.5 (13.9)	66.4 (14.2)	68.0 (14.3)

Pain: patient assessment of pain.
*All patients with exception of one were Caucasian.
†100% patients were on MTX.
‡P=0.33 (χ^2 test).
§Upper limit of normal: >6 mg/L.
¶Joint counts were assessed based on 66–68 joint counts.
anti-CCP+, anticyclic citrullinated peptide positivity; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28-CRP, Disease Activity Score 28 based on C reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; ITT, intention-to-treat; MTX, methotrexate; N, number of subjects; OKZ, olokizumab; PBO, placebo; PGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF+, rheumatoid factor positivity; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor; VAS, Visual Analogue Scale.

Table 2 Efficacy results in the intent-to-treat population (NRI)

	OKZ every 2 weeks N=143	OKZ every 4 weeks N=142	PBO N=143
ACR20 response, n (%), week 12 (primary endpoint)	91 (63.6)*	100 (70.4)*	37 (25.9)
ACR50 response, n (%), week 24	61 (42.7)*	69 (48.6)*	11 (7.7)
ACR70 response†, n (%), week 24	28 (19.6)	32 (22.5)	3 (2.1)
DAS28-CRP <3.2, n (%), week 12	48 (33.6)*	55 (38.7)*	5 (3.5)
HAQ-DI week 12			
LSM (SE)	−0.54 (0.04)	−0.56 (0.04)	−0.20 (0.04)
Treatment comparison vs PBO LSM difference (SE)	−0.34* (0.06)	−0.36* (0.06)	
97.5% CI for LSM difference	−0.47 to −0.21	−0.49 to −0.23	
CDAI ≤2.8, n (%), week 24	12 (8.4)‡	11 (7.7)‡	0
DAS28-CRP <2.6†, n (%), week 24	31 (21.7)	40 (28.2)	5 (3.5)
DAS28-CRP, change from baseline, week 24 LSM (SE)	−2.5 (0.1)	−2.8 (0.1)	−1.2 (0.1)
Treatment comparison vs PBO LSM difference (SE)	−1.4 (0.1)	−1.7 (0.2)	
97.5% CI for LSM difference	−1.7 to −1.0	−2.0 to −1.4	
CDAI <10†, n (%), week 12	37 (25.9)	40 (28.2)	7 (4.9)

*P value difference from PBO <0.0001.
†Results for other than primary and secondary endpoints were not tested for significance.
‡P value difference from PBO <0.001.
ACR, American College of Rheumatology response; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28 based on C reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least squares mean; N, number of subjects; n, number of responders; NRI, non-responder imputation; OKZ, olokizumab; PBO, placebo.

0.20 for every 4 weeks, every 2 weeks and PBO groups, respectively (p<0.0001 for both comparisons) (table 2, figure 3).

The ACR50 response at week 24 was achieved by 48.6% of patients on OKZ every 4 weeks, 42.7% on OKZ every 2 weeks and 7.7% on PBO (p<0.0001 for comparisons of OKZ groups vs PBO) (table 2, figure 3).

Disease remission, defined as CDAI ≤2.8, was achieved at week 24 by 7.7% of patients on OKZ every 4 weeks and by 8.4% on OKZ every 2 weeks. No subjects achieved this endpoint in the PBO group (p=0.0003 for OKZ every 4 weeks vs PBO and p=0.0002 for OKZ every 2 weeks vs PBO comparisons) (table 2, figure 3). The percent mean changes in ACR response criteria parameters and CDAI score parameters are presented in online supplemental figure 1. The number of missing observations for key efficacy outcomes is presented in online supplemental table 1. The results of the primary and ranked secondary endpoints were confirmed by predefined sensitivity analyses and a post-hoc linear mixed model analysis (data available on request).

Subgroup analyses of the ACR20 response did not show influence of country, gender, age, weight, body mass index, baseline disease severity, time since diagnosis, duration of prior MTX use, or anticyclic citrullinated peptide and rheumatoid factor status on the efficacy of OKZ (data available on request).

In parallel with the main efficacy endpoints, there were marked increases (improvement) in SF-36 mental component scores from baseline to week 24 of approximately 8.9, 6.2 and 2.5 in patients on OKZ every 4 weeks, OKZ every 2 weeks and PBO, respectively. Corresponding values for SF-36 physical component scores were 8.7, 7.8 and 3.5. Likewise, FACIT-F improvements were 10.6, 8.5 and 3.7 (table 3). Other quality of life measures showed similar trends in improvement (table 3, online supplemental table 2).

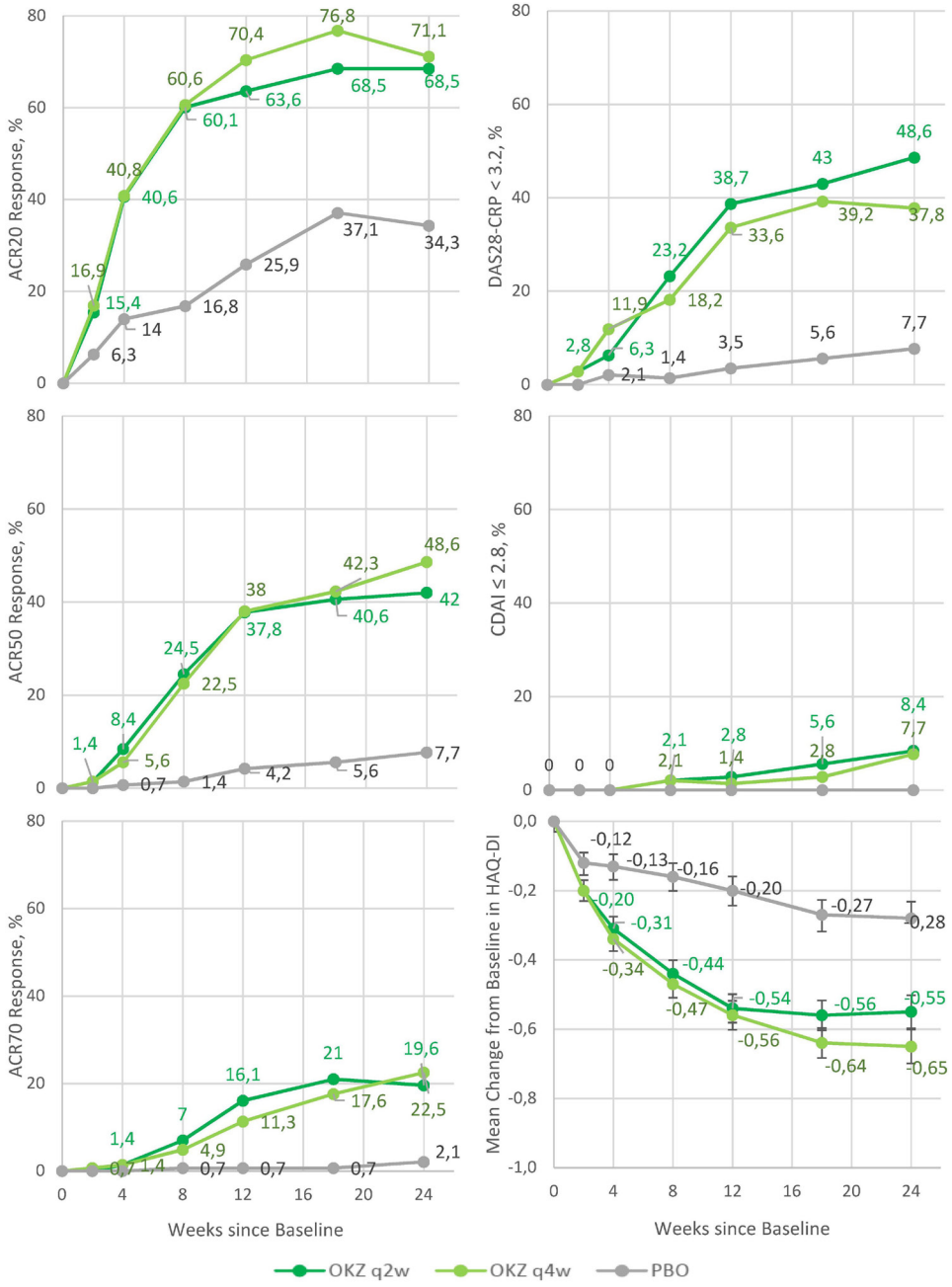

Figure 3 Efficacy results during the double-blind treatment period (ITT population). ACR, American College of Rheumatology response; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28 based on C reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; ITT, intention-to-treat; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks.

Safety

Two hundred and twenty-six patients (52.9%) reported treatment-emergent adverse events (TEAE) with similar incidences across the treatment groups (table 4).

Most TEAEs were mild to moderate in severity and non-serious, leading to study treatment discontinuation in 3.5%, 4.9% and 0.7% of patients on OKZ every 4 weeks, OKZ every 2 weeks and PBO, respectively. The most common TEAEs were investigations reported for 35.9% of patients on OKZ every 4 weeks, 35.0% on OKZ every 2 weeks and 18.3% on PBO, and infections reported for 14.1% on OKZ every 4 weeks, 15.4% on OKZ every 2 weeks and 16.2% on PBO. Injection site reactions were reported by two subjects (1.4%) in each OKZ group. A total of 20 treatment-emergent serious adverse events (TESAEs) were reported.

Incidences of TESAEs were numerically higher in patients on OKZ every 4 weeks and OKZ every 2 weeks, compared with PBO: 5.6%, 5.6% and 2.8%, respectively. The most frequently reported serious events were serious infections: 2.8% in patients on OKZ every 2 weeks and 1.4% on PBO (no serious infections were reported for OKZ every 4 weeks). One TEAE leading to death was reported in the study, septicaemia due to *Staphylococcus aureus* and toxic shock syndrome in the OKZ group every 2 weeks. There were no reports of gastrointestinal perforations or anaphylaxis.

As reported with other anti-IL-6 therapies, there were early rises in mean serum lipids noted from week 4, with a plateau that reached around week 8 (figure 4); however, no MACE was observed. Likewise, early decreases in mean blood platelets and neutrophils were seen, with a plateau reached at week 4. No

Table 3 Patient-reported outcome measures at months 3 (12 weeks) and 6 (24 weeks)*

	Week 12			Week 24		
	OKZ every 2 weeks N=143	OKZ every 4 weeks N=142	PBO N=142	OKZ every 2 weeks N=143	OKZ every 4 weeks N=142	PBO N=142
PtGA	−30.6 (1.7) 17.5 (2.5) −23.0 to −12.0	−31.0 (1.7) −17.9 (2.5) −23.4 to −12.4	−13.1 (1.8)	−32.1 (1.9) −12.7 (2.7) −18.8 to −6.6	−36.3 (2.0) −16.8 (2.8) −23.0 to −10.6	−19.4 (1.9)
Pain	−31.6 (1.8) −18.7 (2.6) −24.6 to −12.9	−31.8 (1.8) −19.0 (2.6) −24.8 to −13.1	−12.8 (1.9)	−34.5 (2.1) −13.0 (2.9) −19.5 to −6.5	−37.1 (2.1) −15.7 (2.9) −22.3 to −9.1	−21.4 (2.1)
Pain, patients with >30% improvement, n (%)	94 (65.7)	86 (60.6)	37 (25.9)	96 (67.1)	95 (66.9)	57 (39.9)
Pain, patients with >50% improvement, n (%)	69 (48.3)	60 (42.3)	18 (12.6)	69 (48.3)	74 (52.1)	25 (17.5)
Pain, patients with level of <10 mm, n (%)	12 (8.4)	13 (9.2)	0 (0.0)	23 (16.1)	24 (16.9)	6 (4.2)
Pain, patients with level of <20 mm, n (%)	38 (26.6)	27 (19.0)	8 (5.6)	41 (28.7)	37 (26.1)	16 (11.2)
Pain, patients with level of <40 mm, n (%)	78 (54.5)	80 (56.3)	29 (20.3)	80 (55.9)	85 (59.9)	41 (28.7)
HAQ-DI†				−0.55 (0.05) −0.27 (0.07) −0.43 to −0.12	−0.65 (0.05) −0.37 (0.07) −0.53 to −0.22	−0.28 (0.05)
HAQ-DI <0.5, n (%)	13 (9.1)	13 (9.2)	2 (1.4)	17 (11.9)	21 (14.8)	5 (3.5)
SF-36 PCS	6.7 (0.6) 4.5 (0.8) 2.7 to 6.3	6.0 (0.6) 3.8 (0.8) 2.0 to 5.6	2.2 (0.6)	7.8 (0.7) 4.3 (0.9) 2.2 to 6.4	8.7 (0.7) 5.2 (1.0) 3.1 to 7.4	3.5 (0.7)
SF-36 MCS	6.5 (0.7) 3.0 (1.0) 0.7 to 5.3	7.0 (0.7) 3.6 (1.1) 1.2 to 5.9	3.5 (0.8)	6.2 (0.8) 3.7 (1.1) 1.2 to 6.2	8.9 (0.8) 6.4 (1.1) 3.8 to 8.9	2.5 (0.8)
EQ-5D score	19.7 (1.7) 12.2 (2.4) 6.8 to 17.6	18.7 (1.7) 11.2 (2.4) 5.8 to 16.7	7.4 (1.7)	20.9 (2.0) 12.6 (2.7) 6.5 to 18.7	23.6 (2.0) 15.3 (2.8) 8.9 to 21.7	8.3 (2.0)
FACIT-F	8.2 (0.7) 4.6 (1.0) 2.4 to 6.8	8.7 (0.7) 5.1 (1.0) 2.9 to 7.3	3.6 (0.7)	8.5 (0.8) 4.8 (1.1) 2.3 to 7.3	10.6 (0.8) 6.9 (1.1) 4.3 to 9.5	3.7 (0.8)

Pain: patient's assessment of arthritis pain.
*With the exception of pain, n (%) LSM change from baseline (SE), treatment comparison vs placebo LSM difference (SE), and 97.5% CI for LSM difference are presented.
†Secondary endpoint (refer to table 2).
EQ-5D, European Quality of Life-5 Dimensions; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale (MCID ≥4 units); HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least squares mean; MCID, minimal clinically important difference; MCS, Mental Component Score (MCID ≥2.5 units); N, number of subjects; OKZ, olokizumab; PBO, placebo; PCS, Physical Component Score (MCID ≥2.5 units); PtGA, Patient Global Assessment of Disease Activity; SF-36, Short Form-36.

patients had grade 3 or higher neutropaenia in accordance with the Common Terminology Criteria for Adverse Events version 4.0. Elevations in serum alanine aminotransferase values above 3× ULN at any time during the study were seen in 11.4%, 9.2% and 5.0% of patients on OKZ every 4 weeks, OKZ every 2 weeks and PBO, respectively, with no concomitant elevations in serum bilirubin above 2× ULN. Selected abnormal haematology and chemistry assessments are presented in online supplemental tables 3 and 4.

Immunogenicity

Positive confirmed ADA tests at any time post baseline were reported in six subjects (4.4%) on OKZ every 2 weeks and in nine subjects (6.6%) on OKZ every 4 weeks. No subjects had a positive result for neutralising antibodies.

DISCUSSION

CREDO 1 trial, a phase III study of OKZ in patients with active RA despite MTX, achieved the primary and all ranked secondary efficacy endpoints. This study evaluated two effective doses with a frequency of injection of once per 2 weeks and once per month, and both regimens of OKZ were superior to PBO in reducing signs and symptoms and improving disability and quality of life over a period of 24 weeks. The onset of efficacy of OKZ was rapid as detected by differences in ACR20 response rates between OKZ and PBO that were apparent within 2 weeks from the start of treatment. The study was specifically designed and sized to detect differences between OKZ and PBO, so small differences seen between OKZ doses in one variable could be by chance, especially since they were not consistently detected across efficacy endpoints. ACR20 was used as the primary endpoint due to its widely accepted and validated value in assessing the efficacy of drugs in RA over many years. While higher levels of response such as ACR50 or ACR70 responses could have been chosen as the primary outcome, use of ACR20 allows for easier comparisons with other compounds evaluated in the past that used ACR20. While ACR20 was the primary endpoint, the study included ACR50 as a ranked secondary endpoint, as well as DAS28-CRP <3.2 and CDAI ≤2.8 (remission), all of which confirmed the results of the ACR20 analysis. In this study patients had relatively high disease activity at baseline, making it more difficult to achieve DAS28-CRP <3.2 status by week 12, as compared with becoming ACR20 responders. Despite this, the data regarding DAS28-CRP <3.2 are consistent with what has previously been reported for anti-IL-6R antibodies, in the same population.[8 9 16]

Disability is an important aspect of RA that originates from joint pain and joint damage and should be directly assessed in RA clinical trials.[17] One of the secondary endpoints in the study was assessment of disability using the HAQ-DI questionnaire.[18 19] The study showed that both regimens of OKZ resulted in significantly more improvement in disability than PBO. Additionally,

Table 4 TEAE by system organ class and preferred term and key serious treatment-emergent adverse events (safety population)

System organ class (preferred term)	OKZ every 2 weeks N=143, n (%)	OKZ every 4 weeks N=142, n (%)	PBO N=142, n (%)
Number of subjects with at least one TEAE reported for 4% of subjects in any treatment group	83 (58.0)	81 (57.0)	62 (43.7)
Investigations	50 (35.0)	51 (35.9)	26 (18.3)
ALT increased	25 (17.5)	33 (23.2)	11 (7.7)
AST increased	16 (11.2)	22 (15.5)	10 (7.0)
White cell count decreased	7 (4.9)	6 (4.2)	4 (2.8)
Neutrophil count decreased	6 (4.2)	7 (4.9)	3 (2.1)
Blood cholesterol increased	6 (4.2)	4 (2.8)	3 (2.1)
Gamma-glutamyltransferase increased	3 (2.1)	6 (4.2)	4 (2.8)
Infections and infestations	22 (15.4)	20 (14.1)	23 (16.2)
Nasopharyngitis	4 (2.8)	3 (2.1)	6 (4.2)
Upper respiratory tract infection	2 (1.4)	6 (4.2)	4 (2.8)
Blood and lymphatic system disorders	17 (11.9)	18 (12.7)	15 (10.6)
Leucopenia	8 (5.6)	7 (4.9)	4 (2.8)
Neutropaenia	5 (3.5)	9 (6.3)	2 (1.4)
Anaemia	4 (2.8)	3 (2.1)	6 (4.2)
Metabolism and nutrition disorders	9 (6.3)	7 (4.9)	3 (2.1)
Musculoskeletal and connective tissue disorders	6 (4.2)	7 (4.9)	6 (4.2)
Skin and subcutaneous tissue disorders	8 (5.6)	3 (2.1)	2 (1.4)
Number and percentage with at least one key TESAE	8 (5.6)	8 (5.6)	4 (2.8)
Investigations	2 (1.4)	4 (2.8)	1 (0.7)
ALT increased	2 (1.4)	4 (2.8)	1 (0.7)
AST increased	0	3 (2.1)	0
Infections and infestations	4 (2.8)	0	2 (1.4)
Subcutaneous abscess	2 (1.4)	0	0
Gastroenteritis	0	0	1 (0.7)
Pneumonia	0	0	1 (0.7)
Pulmonary tuberculosis	1 (0.7)	0	0
Staphylococcal sepsis	1 (0.7)	0	0
Toxic shock syndrome	1 (0.7)	0	0
Herpes zoster	0	0	0
Hepatobiliary disorders	0	1 (0.7)	0
Drug-induced liver injury	0	1 (0.7)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.7)	0
Cervix carcinoma stage II	0	1 (0.7)	0
Gastrointestinal disorders	0	1 (0.7)	0
Obstructive pancreatitis	0	1 (0.7)	0
Gastrointestinal perforation	0	0	0
Vascular disorders	0	1 (0.7)	0
Diabetic vascular disorder	0	1 (0.7)	0
Venous thromboembolism	0	0	0
Death	1 (0.7)	0	0

All AEs were collected from the signature of the informed consent form until the last visit of the subject in the study (up to 22 weeks after the final dose of study treatment) regardless of relationship to study treatment, thus up to approximately 44 weeks.
A TEAE is defined as an AE that first occurred or worsened in severity after the first dose of the study treatment.
%, percentage of subjects calculated relative to the total number of subjects in the population.
MedDRA (Medical Dictionary for Regulatory Activities, V.21.1) was used to code AEs.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, number of subjects with events; N, number of subjects; OKZ, olokizumab; PBO, placebo; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

in this patient population and investigational setting, 89 (62.2%) and 94 (66.2%) patients treated with OKZ had improvement in their HAQ-DI score with more than minimally detectable difference of 0.22, compared with 63 (47.6%) in the PBO group.

Chronic arthritis can have a profound effect on patients' quality of life.[20] In this study it was shown that the improvements seen in signs and symptoms and disability of RA were mirrored by positive effects on quality of life measures including SF-36 and FACIT-F. SF-36 is a multidomain questionnaire that assesses different aspects of a person's life, summarised into PCS and MCS. Treatment with OKZ resulted in improvements across all of these domains (table 3). Certain mental ailments such as sleep disorders and fatigue in RA may be linked to high levels of circulating IL-6.[21 22] OKZ treatment resulted in marked improvements in fatigue, consistent with its mechanism of action as an inhibitor of IL-6.

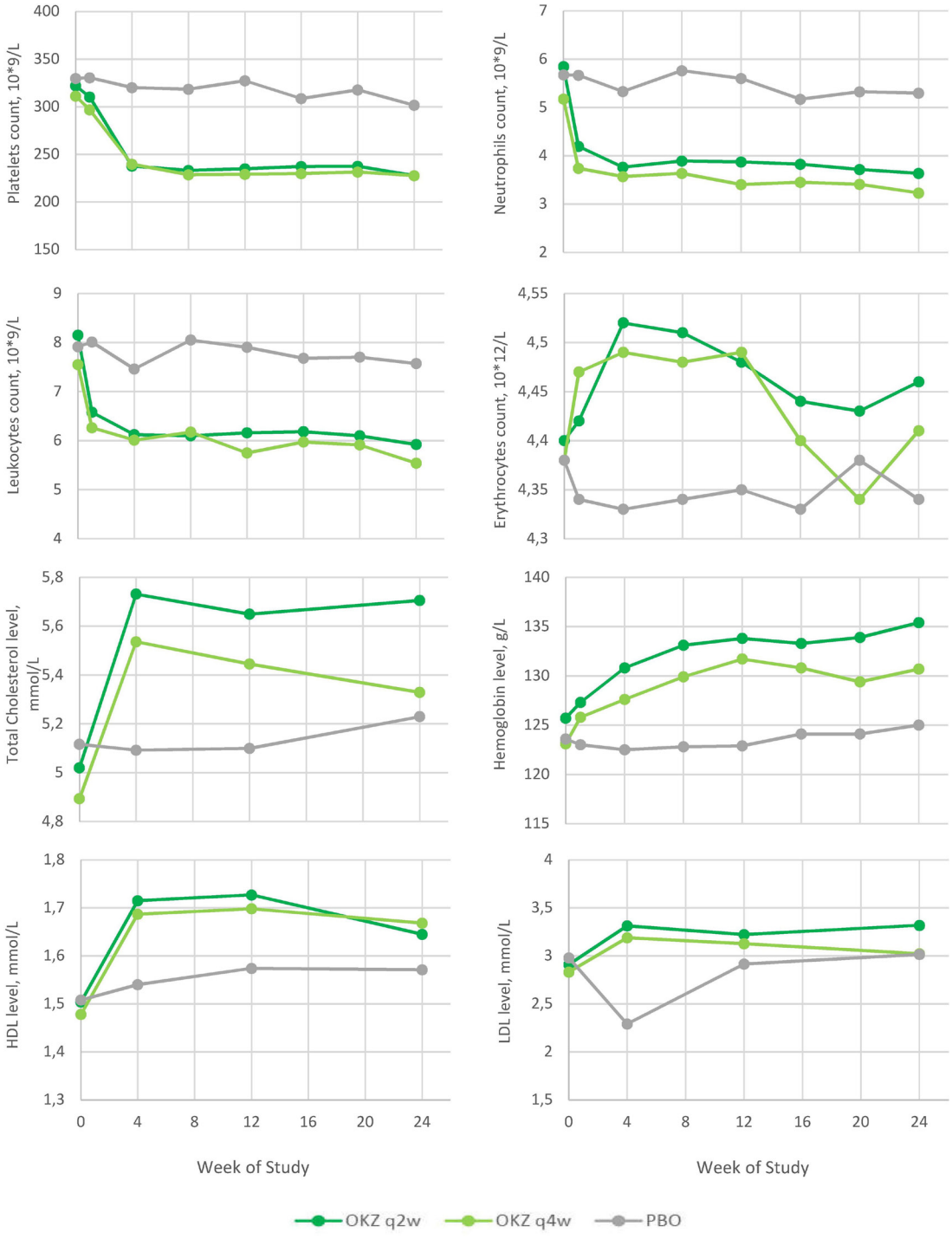

Figure 4 Mean changes in laboratory values during the double-blind treatment period (safety population). HDL, high-density lipoproteins; LDL, low-density lipoproteins; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks.

CREDO 1 trial also evaluated the safety of OKZ over 24 weeks and confirmed that OKZ has a safety profile similar to approved anti-IL-6R antagonists and no unexpected safety findings.[23 24]

As expected, there were more adverse events observed in the OKZ-treated patients, but they were mostly mild to moderate with few serious adverse events and no unexpected safety findings and relatively low number of dropouts due to an adverse event. In this relatively small study few serious infections, including opportunistic infection (pulmonary TB) and one fatal event, were reported for OKZ every 2 weeks and none for OKZ every 4 weeks.

There are several limitations to the study. First, there was no active comparator in this study, limiting the ability to compare with other agents. Second, the study did not include radiographic assessments. An analysis of RA trials of anti-TNF biologics showed a trend towards decreasing rate of radiographic progression, possibly due to more effective patient management, and to reliably show a positive radiographic effect one must include large numbers of patients on PBO, a possible ethical issue.[25] Third, this study was conducted in a limited geographical location with limited racial diversity and its findings should be confirmed in other phase III controlled trials that include a more diverse patient population.

CONCLUSION

In this first phase III trial of OKZ in patients with active RA despite treatment with an adequate dose of MTX, OKZ demonstrated significant improvements in signs and symptoms of RA, including in disability and quality of life measures, compared with PBO. OKZ was reasonably well tolerated over a period of 24 weeks with no unexpected safety findings.

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ONLINE SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS

Randomization and blinding

After eligibility had been confirmed, subjects were randomized by blinded study staff using IWRS (an automated web randomization system). The IWRS allocated the treatment group and assigned the study treatment. This system also managed drug supply management and visit dispensation. Blinded study staff requested study treatment assignment via IWRS for all subsequent treatment study visits. Cenduit Interactive Response Technology (C.I.R.T) system (Cenduit, LLC) was used in the study for this purpose. A top-down randomization was used in a 1:1:1 ratio for the three treatment groups: Olokizumab (OKZ) 64 mg (q4w), OKZ 64 mg (q2w), and Placebo. A block size of 6 was applied.

As this was a randomized, double-blind, placebo-controlled study, access to randomization codes was restricted. The treatment each subject received have not been disclosed to the blinded site staff, including the Investigator, study coordinator, subject, R-Pharm, or R-Pharm's designee. Since the study treatments were distinguishable, they have been prepared by the unblinded pharmacist (or their unblinded designee) out of sight of the subject and any blinded study team members and were provided to blinded site staff in blinded syringes that were identical in appearance. The study site staff have been trained in methods that must be followed and documented to prevent unblinding. Guidance on specific blinding procedures were provided in the Study Reference Manual. The treatment codes were held by the IWRS. Only the unblinded pharmacist (or their unblinded designee) or dedicated unblinded staff who were not directly involved in subject management were aware of the randomized drug assignment. The storage and preparation of study treatment were performed at a secured location that was not accessible to blinded investigational staff. Additional measures to ensure that both Investigators and subjects remained blinded to study treatment included the following:

· Joint assessments have been made by an independent assessor, blinded to both the dosing regimen and all other study assessments.

· Laboratory results for CRP and ESR samples collected during the Treatment Period were not available to blinded study site staff. As ESR was tested locally, the testing have been performed, reviewed, and registered by unblinded study site staff who were not responsible for managing subjects.

· Certain efficacy assessments (ACR20, ACR50, ACR70, DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI) have not been calculated by the Investigator during the course of the study, but were instead computed in the statistical database for analysis purposes.
All blinded procedures have been respected.

Members of the independent DSMB reviewed separately safety data during the study. In the event that ongoing safety monitoring has uncovered an issue needed to be addressed by unblinding at the treatment group level, only members of the DSMB were permitted to conduct additional analysis of the safety data.

Patient inclusion criteria

Subjects could be enrolled in the study only if they had met all of the following criteria:

1. Male or female subjects ≥18 years of age
2. Subjects willing and able to sign informed consent
3. Subjects with a diagnosis of adult-onset RA classified by ACR/EULAR 2010 revised classification criteria for RA for at least 12 weeks prior to Screening
    - If the subject was diagnosed according to ACR 1987 criteria previously, the Investigator could classify the subject per ACR 2010 retrospectively, using available source data
4. Inadequate response to treatment with oral, SC, or intramuscular (IM) MTX (for definition of inadequate response to MTX treatment) for at least 12 weeks prior to Screening at a dose of 15 to 25 mg/week (or ≥10 mg/week if intolerant to higher doses)
    - The dose and means of administering MTX had to be stable for at least 6 weeks prior to Screening
5. Subjects had to be willing to take folic acid or equivalent throughout the study
6. Subjects with moderately to severely active RA disease as defined by all of the following:
    a. ≥6 tender joints (68-joint count) at Screening and baseline; and
    b. ≥6 swollen joints (66-joint count) at Screening and baseline; and
    c. CRP above ULN at Screening based on the central laboratory results

Patient exclusion criteria

Subjects who meet any of the following criteria were eligible for the study:

1. Diagnosis of any other inflammatory arthritis or systemic rheumatic disease (e.g., gout, psoriatic or reactive arthritis, Crohn's disease, Lyme disease, juvenile idiopathic arthritis, or systemic lupus erythematosus)
    - However, subjects could have secondary Sjogren's syndrome or hypothyroidism
2. Subjects who were Steinbrocker class IV functional capacity (incapacitated, largely or wholly bed-ridden or confined to a wheelchair, with little or no self-care)
3. Prior exposure to any licensed or investigational compound directly or indirectly targeting IL-6 or IL-6R (including tofacitinib or other Janus kinases and spleen tyrosine kinase [SYK] inhibitors)
4. Prior treatment with cell-depleting therapies, including anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, and anti-CD19)
5. Prior use of bDMARDs, with the following exception:

- Subjects who discontinued TNFi therapy due to a reason other than lack of efficacy were allowed to enter the study (TNFi therapy should not have been discontinued to facilitate a subject's participation in the study, but should instead have been previously discontinued as part of a subject's medical management of RA). The use of TNFi therapy within the following windows prior to baseline was exclusionary:
    a. 4 weeks for etanercept
    b. 8 weeks for infliximab
    c. 10 weeks for adalimumab, certolizumab, and golimumab

6. Use of parenteral and/or intra-articular glucocorticoids within 4 weeks prior to baseline
7. Use of oral glucocorticoids greater than 10 mg/day prednisone (or equivalent), or change in dosage within 2 weeks prior to baseline
8. Prior documented history of no response to hydroxychloroquine and sulfasalazine
9. Prior use of cDMARDs (other than MTX) within the following windows prior to baseline (cDMARDs should not have been discontinued to facilitate a subject's participation in the study, but should instead have been previously discontinued as part of a subject's medical management of RA):
    a. 4 weeks for sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penicillamine, minocycline, or doxycycline
    b. 12 weeks for leflunomide unless the subject had completed the following elimination procedure at least 4 weeks prior to baseline: Cholestyramine at a dosage of 8 grams 3 times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times daily for at least 24 hours
    c. 24 weeks for cyclophosphamide
10. Vaccination with live vaccines in the 6 weeks prior to baseline or planned vaccination with live vaccines during the study
11. Participation in any other investigational drug study within 30 days or 5 times the terminal half-life of the investigational drug, whichever was longer, prior to baseline
12. Other treatments for RA (e.g., Prosorba Device/Column) within 6 months prior to baseline
13. Use of intra-articular hyaluronic acid injections within 4 weeks prior to baseline
14. Use of non-steroidal anti-inflammatory drugs (NSAIDs) on unstable dose or switching of NSAIDs within 2 weeks prior to baseline
15. Previous participation in this study (randomized) or another study of OKZ
16. Abnormal laboratory values, as defined below:
    a. Creatinine level ≥1.5 mg/dL (132 µmol/L) for females or ≥2.0 mg/dL (177 µmol/L) for males

b. ALT or AST level ≥1.5× ULN

c. Platelets $<100\times10^9$/L ($<100{,}000/mm^3$)

d. White blood cell count $<3.5\times10^9$/L

e. Neutrophil count $<2000\times10^6$/L ($<2000/mm^3$)

f. Hemoglobin level ≤80 g/L

g. Glycosylated hemoglobin (HbA_{1c}) level ≥8%

17. Subjects with concurrent acute or chronic viral hepatitis B or C infection as detected by blood tests at Screening (e.g., positive for hepatitis B surface antigen [HBsAg], total hepatitis B core antibody [anti-HBc], or hepatitis C virus antibody [HCV Ab])

    a. Subjects who were positive for hepatitis B surface antibody (anti-HBs), but negative for HBsAg and anti-HBc, were eligible.

18. Subjects with HIV infection

19. Subjects with:

    a. Suspected or confirmed active TB disease or a history of active TB disease

    b. Close contact (i.e., sharing the same household or other enclosed environment, such as a social gathering place, workplace, or facility, for extended periods during the day) with an individual with active TB within 1.5 years prior to Screening

    c. History of untreated latent TB infection (LTBI), regardless of interferon-gamma release assay (IGRA) result at Screening

        i. Subjects with a history of untreated LTBI could be re-screened and enrolled if they fulfilled all 3 of the following criteria:

            1. Active TB was ruled out by a certified TB specialist or pulmonologist who was familiar with diagnosing and treating TB (as acceptable per local practice);

            2. The subject had completed at least 30 days of LTBI-appropriate prophylaxis prior to baseline with agents recommended as preventative therapy for LTBI according to country-specific/Centers for Disease Control and Prevention (CDC) guidelines (treatment with isoniazid for 6 months was not an appropriate prophylactic regime for this study and it should not have been used); and

            3. The subject was willing to complete the entire course of recommended LTBI therapy.

    d. Positive interferon-gamma release assay (IGRA) result at Screening. If indeterminate, the IGRA could be repeated once during the Screening Period. If there was a second indeterminate result, the subject to be excluded.

        i. Subjects with a positive IGRA result at Screening could be re-screened and enrolled if they fulfilled all 3 of the following criteria:

            1. Active TB was ruled out by a certified TB specialist or pulmonologist who was familiar with diagnosing and treating TB (as acceptable per local practice);

2. The subject had completed at least 30 days of LTBI-appropriate prophylaxis prior to baseline with agents recommended as preventative therapy for LTBI according to country-specific/CDC guidelines (treatment with isoniazid for 6 months was not an appropriate prophylactic regime for this study and it should not be used); and

3. The subject was willing to complete the entire course of recommended LTBI therapy.

ii. If a subject with a positive IGRA result at Screening had documented evidence of completing treatment for LTBI with a treatment regime and treatment duration that was appropriate for this study, the subject could be enrolled without further prophylaxis if recommended by a certified TB specialist or pulmonologist who was familiar with diagnosing and treating TB (as acceptable per local practice) and no new exposure in close contact with an individual with active TB after completing the prophylactic treatment was suspected.

20. Concurrent malignancy or a history of malignancy within the last 5 years (with the exception of successfully treated carcinoma of the cervix in situ and successfully treated basal cell carcinoma and squamous cell carcinoma not less than 1 year prior to Screening [and no more than 3 excised skin cancers within the last 5 years prior to Screening])

21. Subjects with any of the following CV conditions:

    a. Uncompensated congestive heart failure, or class III or IV heart failure defined by the New York Heart Association classification (The Criteria Committee of the New York Heart Association, 1994)

    b. Untreated or resistant arterial hypertension Grade II-III (systolic blood pressure [BP] >160 mm Hg and/or diastolic BP >100 mm Hg)

    c. History or presence of concurrent severe and/or uncontrolled CV disorder (including but not limited to acute coronary syndrome or stroke/transient ischemic attack in the previous 3 months before Screening) that could, in the Investigator's judgment, contraindicate subject participation in the clinical study, or was clinically significant enough in the opinion of the Investigator to alter the disposition of the study treatment, or constituted a possible confounding factor for assessment of efficacy or safety of the study treatment

22. Subjects with a history or presence of any concurrent severe and/or uncontrolled medical condition (including but not limited to respiratory, hepatic, renal, GI, endocrinological, dermatological, neurological, psychiatric, hematological [including bleeding disorder], or immunologic/immunodeficiency disorder[s]) that could, in the Investigator's judgment, contraindicate subject participation in the clinical study, or was clinically significant enough in the opinion of the Investigator to alter the disposition of the study treatment, or constituted a possible confounding factor for assessment of efficacy or safety of the study treatment

23. Uncontrolled diabetes mellitus

24. Subjects with any infection requiring oral antibiotic or antiviral therapy in the 2 weeks prior to Screening or at baseline, injectable anti-infective therapy in the last 4 weeks prior to baseline, or serious or recurrent infection with history of hospitalization in the 6 months prior to baseline
25. Subjects with evidence of disseminated herpes zoster infection, zoster encephalitis, meningitis, or other non-self-limited herpes zoster infections in the 6 months prior to baseline
26. Subjects with planned surgery during the study or surgery ≤4 weeks prior to Screening and from which the subject had not fully recovered, as judged by the Investigator
27. Subjects with diverticulitis or other symptomatic GI conditions that could predispose the subject to perforations, including subjects with a history of such predisposing conditions (e.g., diverticulitis, GI perforation, or ulcerative colitis)
28. Pre-existing central nervous system demyelinating disorders (e.g., multiple sclerosis and optic neuritis)
29. History of chronic alcohol or drug abuse as judged by the Investigator
30. Female subjects who were pregnant, lactating, had lactated within the last 12 weeks, or who were planning to become pregnant during the study or within 6 months of last dose of study treatment
31. Female subjects of childbearing potential (unless permanent cessation of menstrual periods, determined retrospectively after a woman had experienced 12 months of natural amenorrhea as defined by the amenorrhea with underlying status [e.g., correlative age] or 6 months of natural amenorrhea with documented serum follicle-stimulating hormone levels >40 mIU/mL and estradiol <20 pg/mL) who were not willing to use a highly effective method of contraception during the study and for at least 6 months after the last administration of study treatment

    OR

    Male subjects with partners of childbearing potential not willing to use a highly effective method of contraception during the study and for at least 3 months after the last administration of study treatment

    Highly effective contraception was defined as:

    - Female sterilization surgery: hysterectomy, surgical bilateral oophorectomy (with or without hysterectomy), or tubal ligation at least 6 weeks prior to the first dose of study treatment
        - In the case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by documented follow-up hormone level assessment
    - Total abstinence if it was the preferred and constant lifestyle of the subject. Thus, periodic abstinence such as ovulation, symptothermal, postovulation, calendar methods, and withdrawal were not acceptable methods of contraception.

- Male sterilization surgery: at least 6 months prior to Screening (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). For female subjects, the vasectomized male had to be the only partner.
- Placement of established intrauterine device (IUD): IUD copper or IUD with progesterone
- Barrier method (condom and intravaginal spermicide, cervical caps with spermicide, diaphragma with spermicide) in combination with the following: established oral, injected, or implanted hormone methods of contraception or contraceptive patch

32. Subjects with a known hypersensitivity to any component of the OKZ drug product or placebo
33. Subjects with a known hypersensitivity or contraindication to any component of the rescue medication
34. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
35. Subject's unwillingness or inability to follow the procedures outlined in the protocol
36. Other medical or psychiatric conditions or laboratory abnormalities that could increase potential risk associated with study participation and administration of investigational products, or that could affect study results interpretation and, as per the Investigator's judgment, made the subject ineligible

Prior and Concomitant Treatments

Concomitant treatment with MTX was detailed in the protocol. Specifically, at the discretion of the Investigator, the dose of MTX could be reduced once during the study for safety reasons.

Concomitant treatment with folic acid ≥5 mg per week or equivalent was required for all subjects starting by Visit 2 (Week 0). Folic acid or equivalent should not have been taken on the same day as MTX.

Specific treatments prohibited prior to (as applicable) and during the course of the study were described in the Table below. Other medications and non-drug therapies not listed within the table that were considered necessary for the subject's safety and well-being could be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF. All medications/treatments received within 4 weeks prior to the Screening Visit were recorded in the eCRF. Prior MTX and all other treatments for RA for the 6 months prior to the Screening Visit were recorded in the eCRF. Doses, route of applications, duration of treatment, and reasons for prescription are also were recorded.

Table Prohibited Medications

Treatment	Restriction
cDMARDs other than MTX	• Treatment with cDMARDs other than MTX was prohibited during the entire study, with the exception of sulfasalazine and/or hydroxychloroquine, which were permitted as rescue medication for nonresponders starting at Week 14 • Prior use of cDMARDs other than MTX within the following windows prior to baseline was exclusionary (cDMARDs should not have been discontinued to facilitate a subject's participation in the study, but should instead have been previously discontinued as part of a subject's medical management of RA): o 4 weeks for sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penicillamine, minocycline, or doxycycline o 12 weeks for leflunomide unless the subject had completed the following elimination procedure at least 4 weeks prior to baseline: cholestyramine at a dosage of 8 grams 3 times daily for at least 24 hours, or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours o 24 weeks for cyclophosphamide
bDMARDs/ kinase inhibitors	• Treatment with any licensed or investigational biologics directly or indirectly targeting IL-6 or IL-6R (including tofacitinib or other JAK or SYK inhibitors) was prohibited during the entire study and their use prior to Screening was exclusionary. • Treatment with cell-depleting therapies, including anti-CD20 agents or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, and anti-CD19), was prohibited during the entire study and their use prior to Screening was exclusionary. • Treatment with bDMARDs, including TNFi therapy, was prohibited during the entire study and their use prior to Screening was exclusionary.
Corticosteroids	• Treatment with an oral glucocorticoid greater than 10 mg/day prednisone or equivalent or a change in dosage within 2 weeks prior to baseline was exclusionary. • Use of parenteral glucocorticoids within 4 weeks prior to baseline was exclusionary. Use of parenteral glucocorticoids was strongly discouraged during the entire study, but limited use was allowed in the following circumstance: o No more than 2 joints could be injected at or after Week 14 after all study assessments for this time point are performed. The injection should not have to exceed 40 mg methylprednisolone or equivalent cumulative dose. Injected joints had to be rated as having their pre-injection status for the remainder of the study.
NSAIDs	• NSAIDs were prohibited during the entire study with the following exceptions: o Stable doses of NSAIDs were permitted during the study if the subject had received stable doses for ≥2 weeks prior to baseline. Doses of NSAIDs had to be kept constant throughout the entire study unless the Investigator changed the dose for safety reasons. Switching of NSAIDs was not allowed. However, if the subject had an AE that requires discontinuation of the NSAID, an alternative NSAID could be initiated per the local label (if not contraindicated).

Treatment	Restriction
	• Aspirin use at daily doses up to 325 mg was permitted if indicated for CV protection. At this dose, aspirin will not be considered an NSAID.
Analgesics	• Analgesics, including opioids, were prohibited during the entire study with the following exception: • Paracetamol/acetaminophen: Maximum 2000 mg per day (maximum 1000 mg per dose). Paracetamol/acetaminophen was not to be taken within 24 hours prior to joint assessment, including baseline assessment.
Hyaluronic acid	• Intra-articular hyaluronic acid was prohibited during the entire study and its use within 4 weeks prior to baseline was exclusionary.
Vaccination	• Live vaccinations were prohibited during the entire study and their use within 12 weeks prior to baseline was exclusionary.

Abbreviations: AE = adverse event; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; CV = cardiovascular; DMARD = disease-modifying anti-rheumatic drug; IL-6 = interleukin-6; IL-6R = IL-6 receptor; JAK = Janus kinase; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; SC = subcutaneous(ly); SYK = spleen tyrosine kinase; TNFi = tumor necrosis factor-α inhibitor.

Allowed Medications

The following medications were allowed (non-exhaustive list), including clarifications of the above prohibited medications:

- Inhaled corticosteroids
- Topical corticosteroids
- Oral corticosteroids
  - Doses of ≤10 mg/day of prednisone or equivalent were permitted as long as the dose had not been changed within the 2 weeks prior to baseline; dose adjustments were not permitted during the study unless the Investigator changed the dose for safety reasons.
- Intra-articular corticosteroids
  - No more than 2 joints could be injected during the study at or after Week 14, after all study assessments for this time point had been performed. The cumulative dose for both injections should not have to exceed 40 mg methylprednisolone or equivalent. Joints treated with IA corticosteroids had to be rated with their pre-injection status for the remainder of the study and had to be omitted from all subsequent joint assessments.
- NSAIDs
  - The subject must have received a stable dose for ≥2 weeks prior to baseline, and the dose must be kept constant throughout the entire study unless the Investigator changes the dose for safety reasons.
- Analgesic treatment with paracetamol/acetaminophen was permitted up to a maximum dose of 2000 mg per day (maximum 1000 mg per dose) or up to the maximum dose in the local label, whichever was lower. Paracetamol/acetaminophen could not to be taken within 24 hours prior to joint assessment, including baseline assessment.

Rescue Medication Starting at Week 14

Subjects were classified in terms of their response to study treatment at Week 14, with nonresponders defined as all subjects who did not improve by at least 20% in both SJC and TJC (66-68 joint assessment). Nonresponders in all groups were prescribed sulfasalazine and/or hydroxychloroquine according to the local label of the prescribed drug(s) as rescue medication starting at or as close as possible to Week 14, in addition to the assigned study treatment.

The maximum allowed doses of sulfasalazine and hydroxychloroquine were:

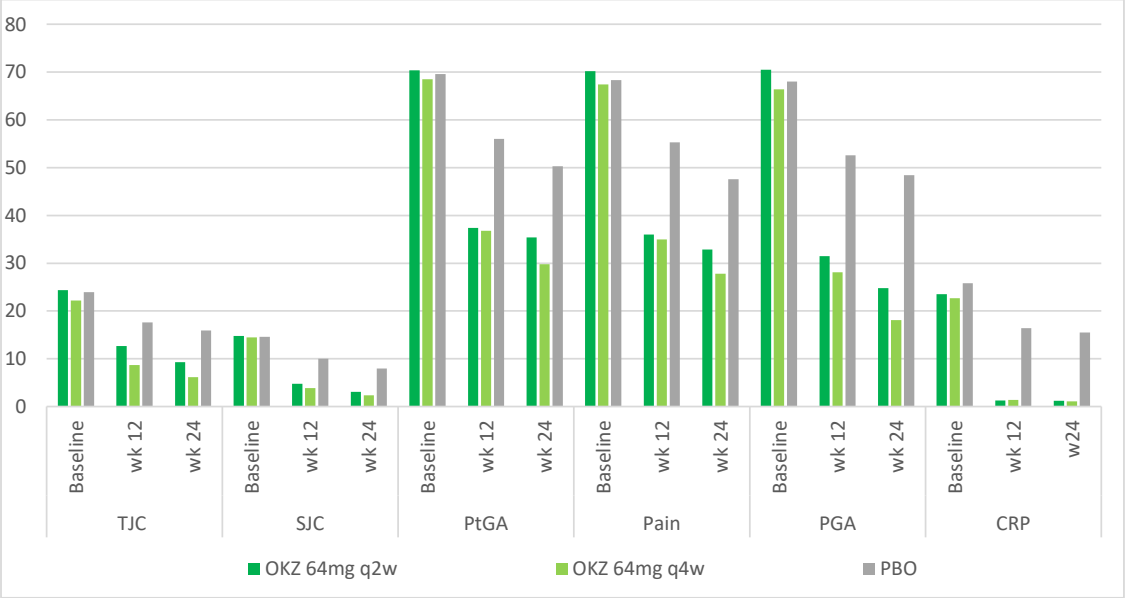
- Sulfasalazine: 3 g per day
- Hydroxychloroquine: 400 mg per day

Nonresponders at Week 14 remained blinded to their assigned treatment. Rescue medication was administered as open-label treatment. The choice of rescue medication (sulfasalazine, hydroxychloroquine, or both) had been made according to local practice, and the assigned rescue medication regimen was maintained throughout the study.

For subjects who receive rescue medication, periodic safety evaluations for toxicity resulting from sulfasalazine and/or hydroxychloroquine were undertaken as per the drug label and local guidelines.

SUPPLEMENTARY FIGURE

Figure S1. **Percent mean changes in ACR response criteria parameters and CDAI score parameters during the double-blind treatment period (ITT population)**



CRP, C-reactive protein; ITT, intention-to-treat; OKZ, olokizumab; PBO, placebo; PGA, physicians' global assessment of disease activity; PtGA, patient's global assessment of disease activity; q2w, every 2 weeks; q4w , every 4 weeks; SJC, swollen joint count (66); TJC, Tender joint count (68); wk, week

SUPPLEMENTARY TABLES

Table S1. **Number of missing observations for key efficacy outcomes (ITT population)**

		OKZ 64mg q2w	OKZ 64mg q4w	Placebo
	Missing data for	N=143	N=142	N=143
Wk 2	ACR20, n(%)	9 (6.3)	6 (4.2)	6 (4.2)
	DAS28-CRP, n(%)	10 (7.0)	9 (6.3)	9 (6.3)
	HAQ-DI, n(%)	8 (5.6)	6 (4.2)	6 (4.2)
	CDAI, n(%)	8 (5.6)	7 (4.9)	6 (4.2)
Wk 4	ACR20, n(%)	7 (4.9)	9 (6.3)	12 (8.4)
	DAS28-CRP, n(%)	8 (5.6)	12 (8.4)	17 (11.9)
	HAQ-DI, n(%)	5 (3.5)	9 (6.3)	12 (8.4)
	CDAI, n(%)	5 (3.5)	9 (6.3)	14 (9.8)
Wk 8	ACR20, n(%)	11 (7.7)	9 (6.3)	18 (12.6)
	DAS28-CRP, n(%)	10 (7.0)	12 (8.4)	24 (16.8)
	HAQ-DI, n(%)	9 (6.3)	9 (6.3)	18 (12.6)
	CDAI, n(%)	11 (7.7)	9 (6.3)	18 (12.6)
Wk 12	ACR20, n(%)	15(10.5)	19(13.3)	18(12.6)
	DAS28-CRP, n(%)	13(9.1)	21(14.7)	18(12.6)
	HAQ-DI, n(%)	13(9.1)	18(12.6)	18(12.6)
	CDAI, n(%)	17(11.9)	20(14.0)	18(12.6)
Wk 18	ACR20, n(%)	18 (12.6)	28 (19.6)	23 (16.1)
	DAS28-CRP, n(%)	26 (18.2)	35 (24.5)	35 (24.5)
	HAQ-DI, n(%)	16 (11.2)	28 (19.6)	23 (16.1)
	CDAI, n(%)	16 (11.2)	29 (20.3)	24 (16.8)

Wk 24	ACR20/50/70, n(%)	42(29.4)	44(30.8)	38(26.6)
	DAS28-CRP, n(%)	43(30.1)	44(30.8)	38(26.6)
	HAQ-DI, n(%)	42(29.4)	44(30.8)	38(26.6)
	CDAI, n(%)	43(30.1)	44(30.8)	38(26.6)

Missing observations are defined as number of missing data and/or number of case "out of Window". ACR, American College of Rheumatology response; CDAI, clinical disease activity index; DAS28-CRP, Disease Activity Score 28 based on C-reactive protein; ITT, Intention-to-treat; HAQ-DI, Health Assessment Questionnaire Disability Index; N, Number of subjects in the analysis population; n (%), Number of subjects with missing data and/or with cases "out of Window"; OKZ, olokizumab; q2w, every 2 weeks; q4w, every 4 weeks; Wk, week

Table S2. **Changes from baseline at months 3 (12 week) and 6 (24 week) for WPS-RA (patient-reported outcome measures)[1]**

	Week 12			**Week 24**		
	OKZ q2w N=143	**OKZ q4w N=142**	**Placebo N= 142**	**OKZ q2w N=143**	**OKZ q4w N=142**	**Placebo N= 142**
WPS-RA Missed Work Days	-11.14(3.6) -10.3(5.2) -22.0,1.4	-13.5(3.3) -12.7(5.1) -24.0,-1.3	-0.9(3.7)	-10.5(3.0) -2.9(4.4) -12.8,6.9	-12.8(3.1) -5.2(4.5) -15.3,4.8	-7.6(3.3)
WPS-RA Missed Household Days	-15.4(1.7) -7.5(2.5) -13.0,-2.0	-17.9(1.7) -10.0(2.5) -15.5,-4.6	-7.8(1.8)	-17.2(2.0) -10.0(2.7) -16.1,-3.8	-18.0(1.9) -10.8(2.8) -17.0,-4.6	-7.2(1.9)
WPS-RA Work Impairment	-21.5(3.2) -12.9(4.6) -23.3,-2.6	-23.8(3.0) -15.2(4.4) -25.0,-5.3	-8.6(3.3)	-22.5(3.3) -12.8(4.8) -23.6,-2.0	-30.1(3.3) -20.4(4.8) -31.2,-9.6	-9.7(3.6)
WPS-RA Household Impairment	-25.1(1.9) -13.7(2.7) -19.8,-7.6	-29.1(1.9) -17.7(2.7) -23.8,-11.6	-11.3(1.9)	-31.6(2.2) -16.1(3.1) -23.0,-9.2	-36.2(2.2) -20.6(3.1) -27.6,-13.7	-15.5(2.2)
WPS-RA Work Day Productivity	-16.7(4.3) -8.3(62) -22.1,5.5	-18.6(3.9) -10.2(5.9) -23.4,3.0	-8.4(4.4)	-14.7(4.2) -7.3(6.0) -20.7,6.1	-22.6(4.1) -15.2(6.0) -28.6,-1.9	-7.4(4.4)
WPS-RA Household Day Productivity	-17.5(2.0) -8.4(2.8) -14.7,-2.0	-19.6(2.0) -10.4(2.8) -16.7,-4.1	-9.2(2.0)	-19.2(2.2) -11.2(3.0) -18.0,-4.4	-22.2(2.1) -14.2(3.1) -21.0,-7.4	-8.0(2.1)

Changes were analyzed using ANCOVA model adjusted for the baseline value of the corresponding parameter; missing data resulted from study withdrawal imputed based on the return to baseline assumption; 1, LSM change from baseline (SE), treatment comparison vs placebo LSM difference (SE), 97.5% confidential interval for LSM difference are presented. CI, confidence interval; LSM, least squares mean; N, number of subjects in the analysis population; n, number of responders; OKZ, olokizumab; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error; Wk, week; WPS-RA, Work Productivity Survey-Rheumatoid Arthritis.

Table S3**. Patients with selected hematology assessments outside of the normal range (Safety Population)**

			OKZ q2w	**OKZ q4w**	**PBO**
Number of Subjects with			**N=143**	**N=142**	**N=142**
WBC count < 4000/mm^3 (or < 4 ·10^9/L)	BL	Nx(%) n(%)	143(100.0) 2(1.4)	142(100.0) 2(1.4)	142(100.0) 3(2.1)
	Wk 12	Nx(%) n(%)	125(87.4) 16(12.8)	128(90.1) 15(11.8)	129(90.8) 2(1.6)
	Wk 24	Nx(%) n(%)	111(77.6) 16(14.4)	111(78.2) 17(15.3)	115(81.0) 2(1.7)
ANC count < 1500/mm^3 (or < 1.5 ·10^9/L)	BL	Nx(%) n(%)	143(100.0) 0(0.0)	142(100.0) 0(0.0)	142(100.0) 0(0.0)

	Wk 12	Nx(%) n(%)	115(80.4) 1(0.9)	123(86.6) 5(4.1)	125(88.0) 1(0.8)
	Wk 24	Nx(%) n(%)	101(70.6) 3(3.0)	101(71.1) 3(3.0)	112(78.9) 0(0.0)
Hemoglobin ≤80 g/L	BL	Nx(%) n(%)	143(100.0) 0(0)	142(100.0) 0(0)	142(100.0) 0(0)
	Wk 12	Nx(%)	126(88.1)	128(90.1)	129(90.8)
		n(%)	0(0)	0(0)	0(0)
	Wk 24	Nx(%)	111(77.6)	111(78.2)	116(81.7)
		n(%)	0(0)	0(0)	1(0.9)

ANC < 1000/mm^3 (or < 1.0 ·10^9/L) and ALC < 500/mm^3 (or < 0.5 ·10^9/L): no observations. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BL, baseline; N, number of subjects in the arm; Nx(%), number and percent of the subjects with non-missing results; n(%), number and percent of the subjects with abnormal parameters; %, percentage of subjects with non-missing results is calculated relative to the total number of subjects in the population, whilst all other percentages are calculated relative to the number of subjects with non-missing results at a given visit; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; WBC, white blood cells; Wk, week.

Table S4. **Patients with selected chemistry assessments outside of the normal range (Safety Population)**

		OKZ q2w	**OKZ q4w**	**PBO**
Number of subjects with		N=143	N=142	N=142
ALT, n(%) Baseline	Nx >1xULN to≤3xULN >3xULN to≤5xULN >5xULN	143(100.0) 12(8.4) 0 1(0.7)	142(100.0) 14(9.9) 0 0	142(100.0) 14(9.9) 0 0
ALT, n(%) Post-Baseline	Nx >1xULN to≤3xULN >3xULN to≤5xULN > 5x ULN	141(98.6) 67(47.5) 9(6.4) 4(2.8)	140(98.6) 74(52.9) 8(5.7) 8(5.7)	141(99.3) 38(27.0) 6(4.3) 1(0.7)
Cholesterol, n(%) Baseline	Nx High	142(99.3) 53(37.3)	138(97.2) 57(41.3)	141(99.3) 65(46.1)
Cholesterol, n(%) Post-Baseline	Nx High	141(98.6) 105(74.5)	139(97.9) 95(68.3)	140(98.6) 77(55.0)
Cholesterol shifts from normal to high	Wk 12, n(%) Mean change[1],(SD) Wk 24, n(%) Mean change[1],(SD)	40(30.3) 1.3(0.6) 34(30.9) 1.3(0.6)	33(26.4) 1.5(0.7) 33(29.5) 1.5(0.7)	12(9.2) 0.7(0.5) 12(10.3) 1.3(0.8)
LDL Cholesterol, n(%) Baseline	Nx High	142(99.3) 28(19.7)	138(97.2) 36(26.1)	141(99.3) 47(33.3)
LDLCholesterol, n(%) Post-Baseline	Nx High	141(98.6) 82(58.2)	139(97.9) 73(52.5)	140(98.6) 56(40.0)
LDLCholesterol shifts from normal to high	Wk 12, n(%) Mean change[1],(SD) Wk 24, n(%) Mean change[1],(SD)	40(30.5) 1.1(0.6) 34(30.9) 1.2(0.6)	32(25.8) 1.0(0.6) 24(21.4) 1.2(0.6)	12(9.2) 0.6(0.4) 13(11.1) 1.1(0.9)

1, mmol/L; LDL, low density lipoproteins; N, Number of subjects in the population; Nx(%), number and percent of the subjects with non-missing results; n(%), number and percent of the subjects with abnormal parameters; %, percentage of subjects with non-missing results is calculated relative to the total number of subjects in the population, whilst all other percentages are calculated relative to the number of subjects with non-missing results at a given visit; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation; ULN, upper limit of normal; Wk, week