EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2021.19207

Original Article

Long-term safety and efficacy of olokizumab in patients with rheumatoid arthritis and inadequate response to tumor necrosis factor inhibitor therapy in phase II studies

Mark C. Genovese[1], Patrick Durez[2], Roy Fleischmann[3], Yoshiya Tanaka[4], Daniel Furst[5], Hisashi Yamanaka[6], Elena Korneva[7], Igor Vasyutin[7], Tsutomu Takeuchi[8]

ORCID iDs of the authors:
M.C.G. 0000-0001-5294-4503;
P.D. 0000-0002-7156-2356;
R.F. 0000-0002-6630-1477;
Y.T. 0000-0003-0177-3868;
D.F. 0000-0002-4018-7629;
H.Y. 0000-0001-8453-6731;
E.K.0000-0002-4085-5869;
I.V. 0000-0003-0594-7423;
T.T. 0000-0003-1111-8218.

Cite this article as: Genovese MC, Durez P, Fleischmann R, Tanaka Y, Furst D, Yamanaka H, et al. Long-term safety and efficacy of olokizumab in patients with rheumatoid arthritis and inadequate response to tumor necrosis factor inhibitor therapy in phase II studies. Eur J Rheumatol 2021; 8(3): 120-9.

[1] Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, California, USA
[2] Pôle de Pathologies Rhumatismales, Institut de Recherche Expérimentale et Clinique, Cliniques Universitaires Saint-Luc, UCL, Brussels, Belgium
[3] Department of Medicine, University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, Texas, USA
[4] The First Department of Internal Medicine, University of Occupational and Environmental Health School of Medicine, Fukuoka, Japan
[5] The Geffen School of Medicine, University of California, Los Angeles, California, USA
[6] Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan
[7] JSC "R-Pharm", Moscow, Russia
[8] Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

Address for Correspondence: Mark C. Genovese; Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, California, USA

E-mail: genovese@stanford.edu

Submitted: December 05, 2019
Accepted: October 21, 2020
Available Online Date: June 4, 2021

Abstract

Objective: This study aimed to evaluate the long-term safety and efficacy of olokizumab (OKZ), an anti-interleukin (IL)-6 monoclonal antibody, in patients with rheumatoid arthritis (RA) and inadequate response to tumor necrosis factor-alpha inhibitors.

Methods: Eligible patients completed study RA0056, which tested several doses of OKZ, placebo (PBO), and tocilizumab (TCZ) plus methotrexate (MTX) in Western countries, and RA0083 included several doses of OKZ and PBO plus MTX in Asian countries. Both studies were followed by open-label extension (OLE) studies with OKZ 120 mg every 2 weeks, RA0057 and RA0089, respectively. Safety assessments were reported up to 124 weeks in RA0057 and 92 weeks in RA0089. Efficacy assessments were reported up to week 60 in RA0057 and week 52 in RA0089. No formal statistical hypothesis testing was performed, and missing data were not imputed.

Results: A total of 190 patients in RA0057 and 103 patients in RA0089 received OKZ with median treatment duration of 14.1 and 10.1 months, respectively. Serious adverse events (SAEs) were reported in 44 patients (23.2%, 32.7 events per 100 patient-years [PY]) in RA0057 and in 13 patients (12.6%, 23.6 events per 100 PY) in RA0089. Among treatment-emergent adverse events (TEAEs), including SAEs, infections were the most common events. TEAEs leading to withdrawal were reported in 33 (17.4%) patients in RA0057 and in 7 (6.8%) patients in RA0089. Disease activity score 28-joint count on the basis of C-reactive protein level, clinical disease activity index, and simplified disease activity index, as well as the American College of Rheumatology 20%, 50%, and 70% response rates were maintained during the OLE studies, including in those who switched from PBO or TCZ. Improvements in patient-reported outcomes were maintained in OLEs as well.

Conclusion: In the 2 long-term studies, OKZ treatment demonstrated a safety profile expected for IL-6 blocking agents without new safety signals and led to sustained improvements in RA symptoms, physical function, and quality of life.

Keywords: Rheumatoid arthritis, biological products, interleukin-6

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, which is treated with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX) (1, 2). If these therapies are not effective, biologic DMARDs (bDMARDs), such as tumor necrosis factor-alpha (TNF-α) inhibitor, T-cell co-stimulation blockers, B-cell depleting agents, inhibitors of the interleukin-6 (IL-6) receptor, or agents targeting intracellular Janus kinases are recommended (1-3). Despite the availability of these therapies, 30%-50% of the patients treated with bDMARDs or Janus kinase inhibitors fail to achieve low disease activity or remission (4, 5). Olokizumab (OKZ) is a humanized monoclonal antibody being developed for the treatment of patients with RA. It binds directly to IL-6 cytokine and neutralizes its biological activity by blocking hexamer formation on the glycoprotein-130 signaling axis (6).

Clinical efficacy and short-term safety of OKZ have been previously reported in 2 phase IIb randomized controlled trials (RCTs) in patients with RA with inadequate response to anti-TNF therapies: RA0056 (NCT01242488) was conducted in Western countries (7) and RA0083 (NCT01463059) in Asian countries (8). Both the studies were 12-week dose-ranging, double-blind, and double-dummy. Patients in RA0056 received subcutaneous (sc) injections of either placebo (PBO) or OKZ in doses of 60 mg, 120 mg, or 240

mg every 2 weeks (Q2W) or every 4 weeks (Q4W) or intravenous (IV) PBO or IV tocilizumab (TCZ) 8 mg/kg Q4W. The RA0083 study had the same arms, except OKZ 240 mg Q2W, TCZ, and IV PBO. Significantly greater reductions in disease activity score 28-joint count based on C-reactive protein (DAS28-CRP) level from baseline at week 12 compared with PBO were demonstrated, which was the primary endpoint in both trials, with safety profile consistent with approved IL-6 targeting agents and no unexpected safety signals (7, 8). Improvements assessed using DAS28-CRP level were confirmed using clinical disease activity index (CDAI), which does not depend on changes in CRP level (7).

Several phase III studies have been conducted for OKZ to support the safety and efficacy of this compound (NCT02760368, NCT02760433, NCT02760407, and NCT03120949).

Here we report the results of long-term assessments of safety and efficacy of OKZ, including patient-reported outcomes (PROs) from the open-label extension (OLE) studies.

Methods

Study design

Patients from 55 sites in the United States of America (USA), Belgium, and United Kingdom participating in RCT RA0056 and from 34 sites in Japan, Korea, and Taiwan participating in RCT RA0083 were eligible for enrolment in long-term OLE trials RA0057 (NCT01296711) and RA0089 (NCT01533714), respectively. Week 12 of the RCTs was considered as the baseline visit for the OLE studies.

In both the OLE studies, patients received 120 mg of OKZ sc Q2W plus MTX. Dosing in trials was planned to be continued until approval of the marketing application with safety follow-up assessments at 6 and 12 weeks after the last dose of OKZ (Figure 1). However, OLEs were conducted between March 2011 and November 2013 and were prematurely terminated because of change in sponsorship, which was unrelated to any safety or efficacy observations.

The studies were conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, local regulations (Europe, USA, Japan, Korea, and Taiwan), and ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

Inclusion and exclusion criteria for the RCTs have been published previously (7, 8). Briefly, at RCT entry, adults with RA and inadequate response to ≥1 of licensed TNF inhibitors who fulfilled the 1987 American College of Rheumatology (ACR) criteria (9) or had a score of ≥6 as defined by the ACR/European League Against Rheumatism classification and diagnostic criteria for RA (10) and had ≥6/68 tender and ≥6/66 swollen joints at screening and baseline and CRP levels ≥1.2-fold above the upper limit of normal (ULN, 6 mg/L) or erythrocyte sedimentation rate >28 mm/hour (Westergren) were enrolled. Patients were required to be on a stable dose of MTX.

After completion of the RCTs, all patients became eligible for enrolment in the OLE studies and were required to continue their stable dose of MTX (RA0057: 12.5-25.0 mg/week; RA0089: 6-16 mg/week in Japan and 7.5-20 mg/week in Korea and Taiwan) for at least 12 more weeks in the OLE studies after which the dose could be reduced.

Main Points

- Olokizumab (OKZ) is a new monoclonal antibody that targets interleukin (IL)-6 and is used in treatment development for patients with rheumatoid arthritis. Data from open-label extensions (OLEs) of 2 randomized controlled phase II trials (RCT) are reported here to enhance general understanding of long-term use of this compound.
- Safety data from OLE studies show a safety profile consistent with that seen during the RCTs and that has been reported with approved anti-IL-6 agents.
- Clinical efficacy of OKZ was persistent during OLE. Patients who were on placebo during RCTs improved upon re-assignment to OKZ in OLE studies and those who were on tocilizumab during RCTs sustained their initial response after re-assignment to OKZ.
- Patient-reported outcomes related to multiple domains are reported for the RCT and OLE and parallel improvements are seen in clinical outcomes.

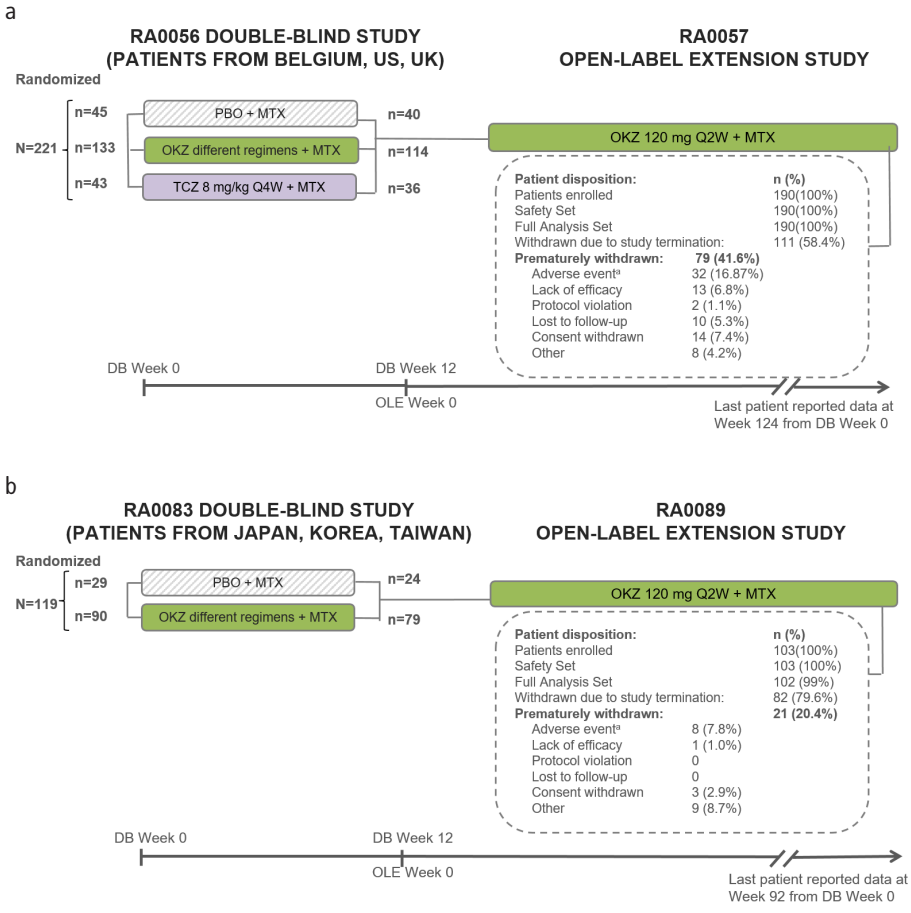

Figure 1. a, b. Patient disposition in the OLE studies RA0057 (a) and RA0089 (b).
[a]For 32 patients from RA0057 study and for 8 patients in RA0089 study, adverse events were reported as the reason for study discontinuation; however, for 2 patients in RA0057 and 1 patient in RA0089, no adverse events leading to treatment withdrawal were reported.
DB: double-blind; OLE: open-label extension; MTX: methotrexate; OKZ: olokizumab; PBO: placebo; TCZ: tocilizumab; Q2W: every 2 weeks; Q4W: every 4 weeks; N: number randomized during RCTs; n: number patients in each treatment group.

The only conventional DMARDs allowed were hydroxychloroquine and sulfasalazine but not before week 24.

Study objectives and evaluations

The primary objective of the OLE studies was to assess the long-term safety of OKZ dose of 120 mg Q2W.

Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, chest X-rays, electrocardiograms, and laboratory parameters. TEAEs, defined as adverse events that started or worsened from OLE baseline and up to 30 days after the last dose of OKZ, were categorized by the medical dictionary for regulatory activities v16.0 primary system organ class and preferred term and were graded according to the common terminology criteria for adverse events v4.0. Serious adverse events (SAEs) were TEAEs that were life-threatening, resulted in hospitalization and significant/persistent disability or death, infections that required treatment with parenteral antibiotics, confirmed cases of active tuberculosis (TB), or other important medical events.

TEAEs are presented here for the period of observation from OLE baseline up to 124 weeks (time point from the RCT baseline) for RA0057 and from OLE baseline and up to 92 weeks (time point from RCT baseline) for RA0089. Laboratory data were summarized for over 60 weeks and 48 weeks from the RCT baseline for RA0057 and RA0089, respectively.

The secondary and exploratory objectives for the OLE studies were evaluation of long-term clinical efficacy and PROs, respectively.

Clinical efficacy variables included DAS28-CRP level, CDAI, simplified disease activity index (SDAI), and ACR 20/50/70 response rates.

The following PROs are reported here: the health assessment questionnaire-disability index (HAQ-DI) (11, 12), patient's global assessment of disease activity visual analogue scale (PtGA) (13, 14), patient's assessment of arthritis pain by visual analogue scale (PAAP) (12), EuroQol 5 dimensions questionnaire (EQ-5D) rating the respondent's current general quality of life (on a 0–100 point scale) (15, 16), and Bristol rheumatoid arthritis fatigue multi-dimensional questionnaire (BRAF-MDQ), which is a 20-item assessment score for fatigue experienced by patients with RA (17).

Changes in the efficacy variables were calculated relative to the RCT baseline (RCT week 0), unless stated otherwise.

Efficacy outcomes are summarized to the last time point at which ≥50% of patients had data (week 60 from the RCT baseline in RA0057 and week 52 from the RCT baseline in RA0089) to allow sufficient number of data points for meaningful reporting.

All time points reported here are calculated from the RCT baseline, except when indicated otherwise.

Statistical analysis

The safety set included all patients who had received ≥1 injection of OKZ in the OLE. Safety data are summarized descriptively and include the number and percentage of patients reporting safety events as well as the incidence rates (the number of events per 100 patient-years [PY] of exposure). Exposure for each patient was calculated as the difference between OKZ treatment start date and end date and presented as median duration of treatment and total exposure in years.

The secondary outcomes were clinical efficacy and PROs on the basis of the full analysis set (FAS) including patients who received ≥1 OKZ dose during the OLE and had ≥1 measurement reported. Only observed efficacy variables were analyzed with no imputation for missing values. Variables calculated as change from the baseline of RCTs were processed only when both the baseline and actual values were available. All results were presented using descriptive statistics.

Minimal clinically important difference (MCID) was defined as follows: reduction in HAQ-DI, ≥0.22 (18, 19); PtGA, score reduction of ≥10 mm (19); PAAP, score reduction of ≥10 mm (19); and BRAF-MDQ, score decrease of ≥17.5% (20). Proportions of patients achieving normative values were calculated for HAQ-DI (<0.5) (21).

All statistical analyses were performed using the Statistical Analysis System® Version 9.1 (SAS Institute Inc.; SAS Campus Drive, Cary, North Carolina, USA) or higher.

Results

Baseline characteristics and disposition

In RA0056, 221 patients were randomized and 190 (86.0%) patients were enrolled in the extension study (114 [60%], 40 [21%], and 36 [19%] patients from OKZ, PBO, and TCZ, groups respectively). In RA0083, 119 patients were randomized and 103 (86.6%) were enrolled in the extension study (79 [77%] patients from OKZ and 24 [23%] patients from PBO group) (Figure 1). The safety set included all the patients enrolled in the OLEs, whereas 102 of 103 patients in RA0089 were included in the FAS (Figure 1).

Demographic and disease characteristics at the RCTs baseline for all patients enrolled in OLEs were generally similar between groups (Table 1). Other baseline characteristics for population enrolled in RCTs have been previously published (7, 8).

The median durations of treatment were 14.1 months in the RA0057 and 10.1 months in RA0089. Total OKZ exposure was 213 PY in RA0057 and 80.5 PY in RA0089. In RA0057, 42.3% of patients received OKZ for <12 months, 29.3% for ≥12 months and <18 months, 19.7% for ≥18 months and <24 months, and 8.7% for > 24 months. In RA0089, 63.2% of patients received OKZ for <12 months, 35.1% for ≥12 months and <18 months, and 1.8% for ≥18 months and <24 months.

During the OLE phase, 79 of the 190 patients (41.6%) in RA0057 and 21 of the 103 patients (20.4%) in RA0089 withdrew from the trial owing to reasons including TEAEs, lack of efficacy, consent withdrawn, and being lost to follow-up (Figure 1).

By week 60, 116 patients remained in RA0057, and by week 52, 56 patients remained in RA0089. In total, 111 patients (58.4%) discontinued RA0057 and 82 patients (79.6%) discontinued RA0089 as a result of study termination (Figures 1 and 2).

Safety

Adverse events

During treatment with OKZ at a dose of 120 mg Q2W, at least 1 TEAE occurred in 176 patients in RA0057 (92.6%, 680.1 events per 100 PY) and in 91 patients in RA0089 (89.2%, 747.2 events per 100 PY). TEAEs classified as SAEs were experienced by 44 patients (23.2%, 32.7 events per 100 PY) in RA0057 and by 13 patients (12.6%, 23.6 events per 100 PY) in RA0089 (Table 2).

The most frequently reported TEAEs in both OLE studies were infections and infestations reported in 125 patients (65.8%, 158.0 events per 100 PY) in RA0057 and in 64 patients (62.7%, 179.0 events per 100 PY) in RA0089 (Table 2). The most common infections were upper respiratory tract infection in RA0057 (35 patients, 18.4%, 21.5 events per 100 PY) and nasopharyngitis in RA0089 (32 patients, 31.4%, 55.9 events per 100 PY).

Serious adverse events

Across both the studies, the most common SAEs were infections that occurred in 15 pa-

Table 1. Patient demographics and disease characteristics for the patients enrolled to OLEs (Safety Set) at the RCTs baseline.

	RA0057			RA0089	
	RA0056 PBO (n=40)	RA0056 OKZ (n=114)	RA0056 TCZ (n=36)	RA0083 PBO (n=24)	RA0083 OKZ (n=79)
Age, median years (min-max)	60.0 (27.0-81.0) [n=40]	55.0 (24.0-82.0) [n=114]	57.0 (33.0-80.0) [n=36]	53.0 (35.0-72.0) [n=24]	56.0 (28.0-77.0) [n=79]
Female, n (%)	33 (82.5)	97 (85.1)	31 (86.1)	21 (87.5)	67 (84.8)
DAS28-CRP, median (min-max)	5.58 (4.16-7.18) [n=40]	6.00 (3.65-8.20) [n=113]	5.74 (3.90-7.59) [n=35]	5.21 (3.44-7.14) [n=24]	5.37 (3.67-7.96) [n=79]
DAS28-CRP >5.1, n (%)	27 (67.5)	84 (74.3)	28 (80.0)	13 (54.2)	53 (67.1)
TJC, (0-28) median (min-max)	15.78 (6.00-28.00) [n=40]	17.00 (4.00-28.00) [n=114]	15.54 (2.00-28.00) [n=36]	9.50 (3.00-23.69) [n=24]	9.00 (2.00-28.00) [n=79]
SJC, (0–28) median (min-max)	9.35 (3.00-22.00) [n=40]	12.00 (1.08-26.00) [n=114]	9.85 (5.00-23.00) [n=36]	9.00 (3.00-24.00) [n=24]	8.62 (4.00-26.00) [n=79]
CDAI, median (min-max)	36.65 (19.00-60.00) [n=40]	42.80 (16.40-71.20) [n=113]	35.60 (17.70-62.50) [n=35]	32.05 (12.60-58.40) [n=24]	30.00 (19.10-70.40) [n=79]
SDAI, median (min-max)	37.13 (20.90-60.10) [n=40]	44.00 (16.50-78.40) [n=113]	36.90 (18.30-67.20) [n=35]	32.85 (16.80-65.80) [n=24]	32.90 (20.04-75.60) [n=79]
HAQ-DI, median (min-max)	1.44 (0.00-2.63) [n=40]	1.63 (0.00-3.00) [n=114]	1.63 (0.00-2.88) [n=36]	1.00 (0.00-2.25) [n=24]	1.13 (0.00-3.00) [n=79]

OLE: open-label extension; RCT: randomized controlled trial; (n): patients enrolled from core study; [n]: total number for calculation; SD: standard deviation; OKZ: olokizumab; PBO: placebo; TCZ: tocilizumab; DAS28-CRP: disease activity score 28 joints (C-reactive protein); TJC: tender joint count; SJC: swollen joint count; CDAI: clinical disease activity index; SDAI: simplified disease activity index; HAQ-DI: health assessment questionnaire-disability index.

tients (7.9%, 8.0 events per 100 PY) in RA0057 and in 7 patients (6.8%, 8.7 events per 100 PY) in RA0089 (Table 2). There was 1 report (1%, 1.2 events per 100 PY) of an SAE of pulmonary TB in a 56-year old woman from Taiwan, which was reported 32 weeks after enrolment in RA0089 and 4 weeks after the last dose of OKZ during the safety follow-up period. The patient had no history of active or latent TB, chronic productive cough, persistent fever, or persistent asthenia. Negative results of purified protein derivative skin test and interferon-gamma release assay (QuantiFERON-TB Gold test) had been provided approximately 3 years before the symptoms of pulmonary TB. The patient completed the entire anti-TB treatment course, and the event was reported as resolved.

In RA0057, cardiac disorders in 5 patients (2.6%, 2.8 events per 100 PY) were reported as SAEs. There were 2 cases of acute myocardial infarction and 1 each of angina pectoris accompanied by electrocardiogram (ECG) changes and troponin-I elevation (no revascularization procedure was reported), bradycardia, and coronary disease with no reports of troponin-I elevation or ECG changes (treatment included revascularization procedure within several weeks after event onset). In RA0057, SAEs related to vascular disorders were reported in 4 patients (2.1%, 1.9 events per 100 PY) and included 1 case of deep vein thrombosis, 1 of hematoma, and 2 of hypertension. No such SAEs were reported in RA0089 (Table 2).

In RA0057, there were 7 reports of malignancies in 5 patients (2.6%, 3.3 events per 100 PY): 1 case of bladder cancer, 1 of stage IV B-cell lymphoma, 1 of renal-cell carcinoma, and 4 of non-melanoma skin cancer. In RA0089, 1 malignancy, a case of non-Hodgkin's lymphoma, was reported (1.0%, 1.2 events per 100 PY).

Sigmoid diverticulitis and diverticular perforation were reported in a 64-year old woman without a prior history of diverticulitis in RA0057 (0.5%, 0.5 events per 100 PY) (Table 2).

In RA0057, 2 (1.1%, 0.935 events per 100 PY) patients died; 1 patient, a 63-year old man, experienced necrotizing fasciitis of the right thigh after approximately 8 months of exposure to OKZ and was subsequently hospitalized. Additional events of sepsis, acute renal failure, and multi-system organ failure were also reported for this patient. The second death occurred in a 56-year old man because of a motor vehicle accident.

Treatment-emergent adverse events leading to discontinuation of OKZ

A total of 33 patients (17.4%) in RA0057 and 7 patients (6.8%) in RA0089 experienced TEAEs leading to permanent discontinuation of OKZ. The most common reasons leading to discontinuation in RA0057 were laboratory investigations (13 patients), including 7 patients with reports of elevated liver function tests. In RA0089, the most frequent adverse events leading to permanent discontinuation were respiratory and skin disorders (2 patients each).

Laboratory abnormalities

Mean changes in laboratory parameters over time from RCTs baseline are presented in Figure 3. There was an initial increase in mean total, low-density, and high-density lipoprotein cholesterol from the baseline of RCTs in patients who received OKZ or TCZ, but during the OLE studies, they were generally stable. An initial decrease from baseline in platelet and neutrophil counts were observed followed by stable but decreased levels over time. Similarly, after an increase from the start of the treatment, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels were stable. Hemoglobin levels initially increased and subsequently remained stable in OLE studies. In the PBO arm of the studies, the same changes were observed in patients from OLE baseline only when OKZ treatment was started.

No abnormalities met the criteria for Hy's law (that is, AST or ALT >3×ULN and bilirubin >2×ULN).

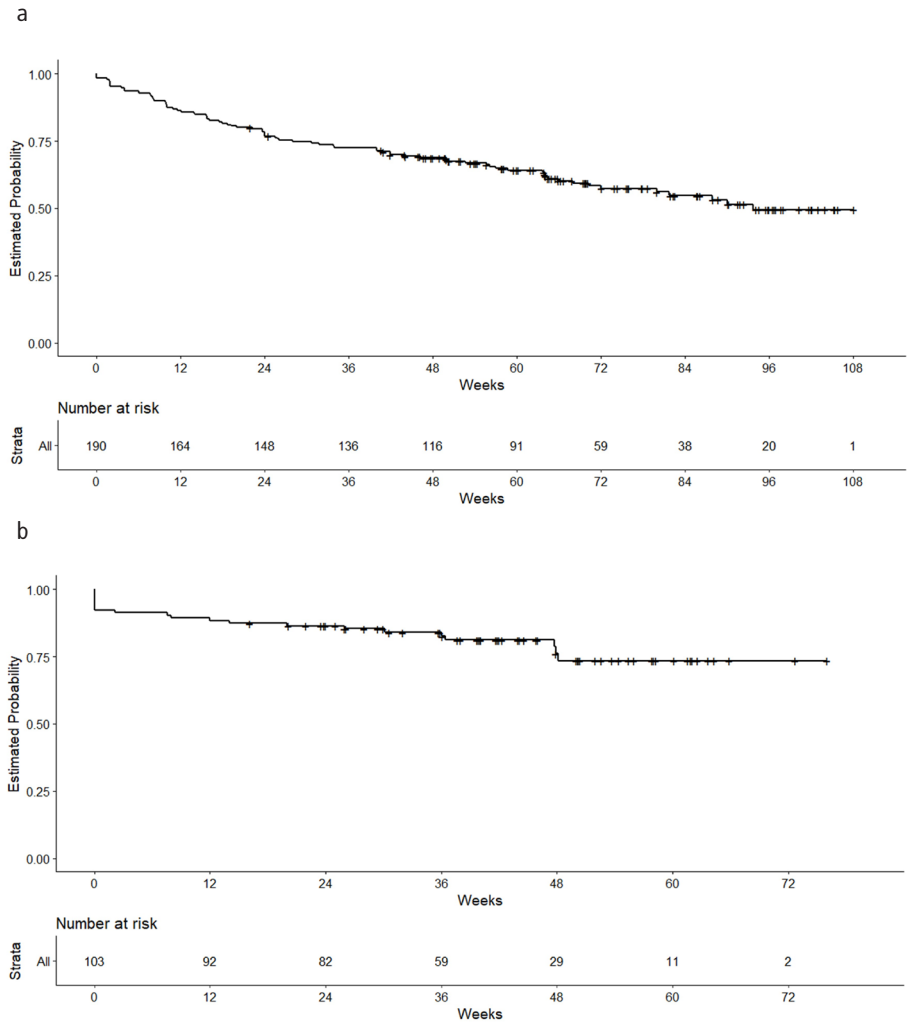

Figure 2. a, b. Kaplan-Meier plots for patient retention in the study and OKZ exposure Kaplan-Meier curve for retention of patients in open-label extension (OLE) studies RA0057 (a) and RA0089 (b). Week 0 indicates OLE week 0 (RCT week 12). Events denoted as + in both graphs indicate censorship of patients who discontinued treatment owing to study termination.
OKZ: olokizumab; OLE: open-label extension; RCT: randomized controlled trial.

Efficacy

Clinical efficacy

In these OLE studies, clinical improvements observed in the OKZ or TCZ (for RA0056 study) arms of the preceding RCTs (7, 8) were generally maintained to week 60 in RA0057 and to week 52 in RA0089 (Table 3). Patients who received PBO in the RCTs had improvements in efficacy outcomes after switching to OKZ at OLE entry, similar to patients randomized to active arms in RCTs.

Similar reductions in CDAI and SDAI at the end of the observational period in OLEs were reported regardless of the treatment arm that the patients were assigned to during the RCTs. Furthermore, in general, the comparable proportions of patients randomized to PBO during RCTs achieved DAS28 scores ≤3.2 or <2.6 by the end of observation period of the OLE studies as those randomized to OKZ or TCZ (study RA0056 only) (Table 3).

ACR responses and DAS28-CRP levels <2.6 and ≤3.2 are shown in Table 3 through week 60 in RA0057 and week 52 in RA0089 for those patients remaining in the study at each time point with variation between the 2 studies. Consistent responses were shown for other clinical metrics with variation between RA0057 and RA0089.

Patient-reported outcomes and responder analyses

OKZ- and TCZ-treated patients (for RA0056 only) demonstrated greater improvement from baseline in physical function assessed by HAQ-DI than patients receiving PBO; for patients in the PBO arms, improvement in HAQ-DI was reported within the OLE studies after switching to OKZ (Table 4). Similar trends were observed for the PtGA, PAAP scores, EQ-5D visual analogue score, and BRAF-MDQ score (Table 4).

Greater proportions of OKZ- and TCZ-treated patients (RA0056 only) reported improvements MCIDs in HAQ-DI at week 12 than patients who received PBO, a difference that was still present at week 60 of RA0057 and week 52 of RA0089 (Table 4). Similar observations were reported for PtGA, PAAP, and BRAF-MDQ; although in RA0089 at week 52, values of PAAP and BRAF-MDQ for patients initially treated with PBO were close to or even slightly higher than (for BRAF-MDQ) for patients who received OKZ in RCT (Table 4).

Discussion

It is well established that IL-6 plays an important role in the pathogenesis of RA (22-24). OKZ is a new anti-IL-6 monoclonal antibody in development for the treatment of RA. In contrast to the currently marketed anti-IL-6 biologics that bind to IL-6 receptor, OKZ binds directly to IL-6.

It was previously shown in 2 short phase II RCTs that OKZ was significantly superior to PBO, with an acceptable safety profile, in patients with RA who had failed 1 or more anti-TNF agents. This study reported the results of the OLE of phase II studies. Although these studies were open-label and included only 1 dose of OKZ 120 mg Q2W, they provided valuable data related to long-term safety and maintenance of efficacy, both important for any new agent being tested for long-term administration (25).

Our data demonstrate that patients who responded to and tolerated OKZ in the RCT continued to do so in the OLE with a safety profile similar to currently available anti-IL-6 biologic agents (26-28).

The rates of SAEs (events/100 PY) in these studies were consistent with the rates reported for other anti-IL-6 therapies (26, 28-30). As reported with a number of biologic agents, infection was the most common TEAE (26, 28, 29). Similarly, the occurrence of events, such as cardiovascular disorders, malignancies, and gastrointestinal perforations, were generally similar to that of previous reports from the OLE studies of other IL-6 blockers (26, 31). No unexpected safety events were reported in these 2 OLE studies.

PROs reflect the patients' perspectives about their well-being and help to describe RA dynamics, both in clinical trials and in practice (32). In line with clinical efficacy variables, improvements in PROs were seen during the RCTs that were maintained during the OLEs. Patients who switched from PBO to OKZ at OLE entry reported numerically less improvements in PROs than patients who were initially allocated to OKZ.

Table 2. Summary of patient exposure, TEAEs occurring in more than 10% of patients, and all SAEs from OLE studies baseline.

MedDRA (v16.0) SOC, PT	RA0057 (N=190)		RA0089 (N=103)	
	Patients n (%)	Events/100 PY	Patients n (%)	Events/100 PY
Patients exposure[a] (PY)	213.9		80.5	
Any AE	176 (92.6)	680.1	91 (89.2)	747.2
Infections and infestations	125 (65.8)	158.0	64 (62.7)	179.0
Upper respiratory tract infection	35 (18.4)	21.5	8 (7.8)	17.4
Urinary tract infection	26 (13.7)	27.6	3 (2.9)	3.7
Bronchitis	19 (10.0)	10.8	4 (3.9)	6.2
Nasopharyngitis	17 (8.9)	11.7	32 (31.4)	55.9
Musculoskeletal and connective tissue disorders	83 (43.7)	84.1	18 (17.6)	29.8
Back pain	20 (10.5)	9.3	2 (2.0)	2.5
Rheumatoid arthritis	20 (10.5)	10.8	0	-
Arthralgia	19 (10.0)	15.0	2 (2.0)	2.5
Gastrointestinal disorders	63 (33.2)	52.8	43 (42.2)	93.2
Diarrhea	19 (10.0)	9.8	6 (5.9)	7.5
Stomatitis	1 (0.5)	0.5	13 (12.7)	26.1
General disorders and administration site conditions	61 (32.1)	84.6	19 (18.6)	92.0
Injection site reaction	21 (11.1)	14.0	3 (2.9)	6.2
Respiratory, thoracic, and mediastinal disorders	57 (30.0)	49.5	22 (21.6)	37.3
Cough	25 (13.2)	15.4	9 (8.8)	14.9
Investigations	56 (29.5)	55.2	18 (17.6)	49.7
Skin and subcutaneous tissue disorders	50 (26.3)	33.2	26 (25.5)	58.4
Injury, poisoning, and procedure complication	41 (21.6)	35.5	23 (22.5)	41.0
Nervous system disorders	32 (16.8)	32.3	18 (17.6)	32.3
Metabolism and nutrition disorders	23 (12.1)	13.1	11 (10.8)	16.2
Vascular Disorders	21 (11.1)	10.8	10 (9.8)	12.4
Neoplasms benign, malignant and unspecified [b]	16 (8.4)	8.9	3 (2.9)	3.7
Eye disorders	13 (6.8)	8.9	14 (13.7)	23.6
SAEs	44 (23.2)	32.7	13 (12.6)	23.6
Infections and infestations	15 (7.9)	8.0	7 (6.8)	8.7
Respiratory, thoracic, and mediastinal disorders	6 (3.2)	4.2	2 (1.9)	2.5
Musculoskeletal and connective tissue disorders	6 (3.2)	2.8	0	-
Neoplasms - benign, malignant, and unspecified	5 (2.6)	3.3	1 (1.0)	1.2
Cardiac disorders	5 (2.6)	2.8	0	-
General disorders and administration site conditions	4 (2.1)	2.3	0	-
Injury, poisoning, and procedural complications	4 (2.1)	2.3	3 (2.9)	6.21
Vascular disorders	4 (2.1)	1.9	0	-
Psychiatric disorders	2 (1.1)	1.4	0	-
Gastrointestinal disorders	1 (0.5)	0.5	2 (1.9)	2.5
Endocrine disorders	1 (0.5)	0.5	0	-
Investigations	1 (0.5)	0.9	0	-
Nervous system disorders	1 (0.5)	0.5	2 (1.9)	2.5
Renal and urinary disorders	1 (0.5)	0.5	0	-
Skin and subcutaneous tissue disorders	1 (0.5)	0.5	0	-
Surgical and medical procedures	1 (0.5)	0.5	0	-
Deaths	2 (1.1)	0.9	0	-

[a] Exposure was calculated as the difference between start and end dates of OKZ treatment, including both RCT and OLE studies; TEAEs occurring in ≥10% of patients in the safety set in either OLE study by preferred term. [b] Including cysts and polyps.

OKZ: olokizumab; OLE: open-label extension; TEAE: treatment-emergent adverse event; SAE: serious adverse event; AE: adverse event; PY: patient-years; SOC: system organ class; PT: preferred term; MedDRA: medical dictionary for regulatory activities.

Table 3. Clinical efficacy of OKZ during OLE studies (full analysis set).

	RA0056/57 week 60			RA0083/89 week 52	
	PBO→OKZ (N=40)	OKZ→OKZ (N=114)	TCZ→OKZ (N=36)	PBO→OKZ (N=24)	OKZ→OKZ (N=78)
Mean change from RCT baseline (SD)					
DAS28-CRP	-2.2 (1.5) [n=20]	-2.4 (1.2) [n=67]	-2.8 (1.3) [n=22]	-3.4 (0.7) [n=14]	-3.2 (1.0) [n=42]
CDAI	-21.4 (16.2) [n=20]	-24.5 (14.0) [n=68]	-24.5 (13.5) [n=22]	-30.2(9.6) [n=14]	-25.0 (10.6) [n=42]
SDAI	-22.7 (16.5) [n=20]	-25.7 (14.6) [n=67]	-27.0 (14.3) [n=22]	-32.6 (10.2) [n=14]	-27.4 (10.8) [n=42]
n (%)					
DAS28-CRP <3.2	9 (45.0) [n=20]	32 (47.8) [n=67]	17 (77.3) [n=22]	12 (85.7) [n=14]	39 (92.9) [n=42]
DAS28-CRP <2.6	6 (30.0) [n=20]	26 (38.8) [n=67]	8 (36.4) [n=22]	8 (57.1) [n=14]	31 (73.8) [n=42]
ACR20 response	10 (50.0) [n=20]	45 (66.2) [n=68]	18 (78.3) [n=23]	12 (85.7) [n=14]	38 (90.5) [n=42]
ACR50 response	6 (30.0) [n=20]	26 (38.2) [n=68]	12 (52.2) [n=23]	10 (71.4) [n=14]	27 (64.3) [n=42]
ACR70 response	4 (20.0) [n=20]	12 (17.6) [n=68]	5 (21.7) [n=23]	7 (50.0) [n=14]	17 (40.5) [n=42]

OLE: open-label extension; OKZ: olokizumab; PBO: placebo; TCZ: tocilizumab; DAS28-CRP: disease activity score 28 (C-reactive protein); CDAI: clinical disease activity index; SDAI: simple disease activity index; ACR20/50/70: American College of Rheumatology 20%/50%/70% response rates.

Table 4. Patient-reported outcomes during RCTs and their respective OLE studies RA0057 and RA0089.

	RCT RA0056/RA0057			RCT RA0083/RA0089		
	Week 0	Week 12	Week 60	Week 0	Week 12	Week 52
HAQ-DI						
Mean (SD)						
PBO	1.5 (0.7) [40]	1.5 (0.7) [n=40]	1.3 (0.8) [n=21]	1.0 (0.7) [n=24]	1.0 (0.7) [n=24]	0.7 (0.9) [n=14]
OKZ	1.6 (0.6) [114]	1.3 (0.7) [n=114]	1.2 (0.7) [n=70]	1.1 (0.6) [n=78]	0.7 (0.7) [n=78]	0.5 (0.6) [n=42]
TCZ	1.6 (0.6) [36]	1.3 (0.6) [n=36]	1.2 (0.7) [n=23]	N/A	N/A	N/A
Mean (SD) change from RCT baseline						
PBO	N/A	0.07 (0.5)	-0.15 (0.7)	N/A	0.00 (0.2)	-0.28 (0.5)
OKZ	N/A	-0.32 (0.5)	-0.45 (0.5)	N/A	-0.41 (0.4)	-0.60 (0.5)
TCZ	N/A	-0.35 (0.3)	-0.43 (0.5)	N/A	N/A	N/A
Patients, n/N (%) ≥MCID						
PBO	N/A	9/40 (22.5)	6/21 (28.6)	N/A	4/24 (16.7)	7/14 (50.0)
OKZ	N/A	64/114 (56.1)	45/70 (64.3)	N/A	55/78 (70.5)	33/42 (78.6)
TCZ	N/A	23/36 (63.9)	17/23 (73.9)	N/A	N/A	N/A
Patients n (%) ≤normative values						
PBO	4/40 (10.0)	4/40 (10.0)	5/21 (23.8)	6/24 (25.0)	7/24 (29.2)	6/14 (42.9)
OKZ	3/114 (2.6)	16/114 (14.0)	11/70 (15.7)	12/78 (15.4)	35/78 (44.9)	22/42 (52.4)
TCZ	2/36 (5.6)	4/36 (11.1)	3/23 (13.04)	N/A	N/A	N/A
PtGA						
Mean (SD)						
PBO	57.5 (22.0) [n=40]	57.4 (26.0) [n=40]	40.4 (23.2) [n=20]	51.2 (18.9) [n=24]	48.3 (18.8) [n=24]	27.7 (22.4) [n=14]
OKZ	60.4 (21.7) [n=111]	41.6 (24.4) [n=111]	35.5 (22.5) [n=69]	59.9 (19.6) [n=78]	33.2 (18.9) [n=78]	22.8 (15.9) [n=42]
TCZ	59.0 (21.0) [n=35]	32.5 (18.6) [n=35]	29.6 (20.1) [n=22]	N/A	N/A	N/A
Mean (SD) CFB						
PBO	N/A	-0.1 (29.1)	-15.6 (29.8)	N/A	-2.9 (20.3)	-26.0 (23.5)
OKZ	N/A	-18.8 (27.0)	-24.0 (28.1)	N/A	-26.8 (23.9)	-37.5 (24.0)
TCZ	N/A	-26.5 (25.5)	-30.0 (22.6)	N/A	N/A	N/A

Table 4. Patient-reported outcomes during RCTs and their respective OLE studies RA0057 and RA0089. (Continue)

	RCT RA0056/RA0057			RCT RA0083/RA0089		
Patients n/N (%) ≥MCID						
PBO	N/A	14/40 (35.0)	11/20 (55.0)	N/A	7/24 (29.2)	9/14 (64.3)
OKZ	N/A	73/111 (65.8)	48/69 (69.6)	N/A	54/78 (69.2)	34/42 (81.0)
TCZ	N/A	28/35 (80.0)	19/22 (86.4)	N/A	N/A	N/A
PAAP						
Mean (SD)						
PBO	57.1 (23.9) [n=39]	56.7 (25.1) [n=39]	40.4 (27.7) [n=20]	53.4 (19.2) [n=24]	47.0 (21.3) [n=24]	19.7 (14.3) [n=14]
OKZ	62.4 (21.6) [n=113]	42.2 (25.2) [n=113]	35.3 (23.1) [n=69]	58.0 (21.7) [n=78]	32.6 (20.5) [n=78]	23.3 (19.5) [n=42]
TCZ	61.3 (17.1) [n=36]	34.3 (21.0) [n=36]	27.7 (20.9) [n=23]	N/A	N/A	N/A
Mean (SD) change from RCT baseline						
PBO	N/A	-0.4 (29.6)	-13.9 (35.6)	N/A	-6.5 (24.7)	-31.4 (21.9)
OKZ	N/A	-20.2 (27.3)	-26.8 (30.1)	N/A	-25.3 (25.4)	-35.0 (28.9)
TCZ	N/A	-27.1 (23.4)	-35.6 (22.0)	N/A	N/A	N/A
Patients, n/N (%) ≥MCID						
PBO	N/A	13/39 (33.3)	9/20 (45.0)	N/A	8/24 (33.3)	11/14 (78.6)
OKZ	N/A	73/113 (64.6)	51/69 (73.9)	N/A	50/78 (64.1)	34/42 (81.0)
TCZ	N/A	30/36 (83.3)	19/23 (82.6)	N/A	N/A	N/A
EQ-5D, mean (SD)						
PBO	56.3 (18.5) [n=40]	49.7 (25.0) [n=40]	59.6 (24.2) [n=21]	57.3 (19.3) [n=24]	51.2 (17.7) [n=24]	73.2 (16.4) [n=14]
OKZ	53.5 (20.9) [n=113]	64.4 (20.8) [n=113]	72.1 (18.8) [n=69]	53.2 (18.3) [n=78]	66.9 (20.6) [n=78]	75.5 (18.9) [n=42]
TCZ	51.8 (22.2) [n=36]	70.0 (19.9) [n=36]	77.3 (14.8) [n=23]	N/A	N/A	N/A
BRAF-MDQ						
Mean (SD)						
PBO	35.2 (17.4) [n=40]	31.7 (17.7) [n=40]	23.7 (17.8) [n=20]	24.3 (11.4) [n=24]	18.3 (12.5) [n=24]	13.5 (9.5) [n=14]
OKZ	34.8 (16.3) [n=113]	23.4 (15.6) [n=113]	19.5 (15.5) [n=68]	24.0 (11.7) [n=78]	12.5 (8.3) [n=78]	11.7 (8.3) [n=42]
TCZ	34.7 (17.1) [n=35]	21.3 (18.3) [n=35]	21.6 (19.7) [n=23]	N/A	N/A	N/A
Mean (SD) CFB						
PBO	N/A	-3.6 (13.5)	-8.4 (15.3)	N/A	-6.0 (10.4)	-10.7 (10.8)
OKZ	N/A	-11.4 (12.8)	-13.3 (13.2)	N/A	-11.5 (9.8)	-12.4 (11.9)
TCZ	N/A	-13.4 (12.9)	-13.3 (12.5)	N/A	N/A	N/A
Patients n/N (%) ≥MCID						
PBO	N/A	16/40 (40.0)	10/20 (50.0)	N/A	17/24 (70.8)	12/14 (85.7)
OKZ	N/A	83/113 (73.5)	51/68 (75.0)	N/A	64/78 (82.1)	30/42 (71.4)
TCZ	N/A	27/35 (77.1)	17/23 (73.9)	N/A	N/A	N/A

BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multi Dimensional Questionnaire; CFB: change from baseline; EQ-5D: EuroQol 5-Dimensions Questionnaire (αthe visual analogue score is reported here); HAQ-DI: Health Assessment Questionnaire-Disability Index; MCID: minimal clinically important difference; N/A: not applicable; PAAP: Patient's Assessment of Arthritis Pain; PBO: placebo; PtGA: Patient's Global Assessment of Disease Activity; OKZ: olokizumab; OLE: open-label extension; RCT: randomized controlled trial; SD: standard deviation; TCZ: tocilizumab; Week number, from RCT baseline; MCID improvement criteria were: HAQ-DI - score decrease of ≥0.22, 25 BRAF-MDQ - score decrease of 17.5%, PtGA and PAAP - score decrease of ≥10 mm; proportions of patients achieving normative values were calculated for HAQ-DI (<0.5).

The OLE data related to improvements in clinical efficacy and PROs are in line with those reported with other anti-IL-6 biologic agents (33, 34) and provide support for extended use of OKZ.

Our data provided useful information regarding long-term use of OKZ; however, we do acknowledge several limitations. First, our studies were open-label and included only 1 dose of OKZ, thus making it difficult to put the observations into proper context. Second, our sample size was relatively small, and there was gradual attrition of patients for various reasons, including premature termination of trials. Finally, our studies included only patients with pre-

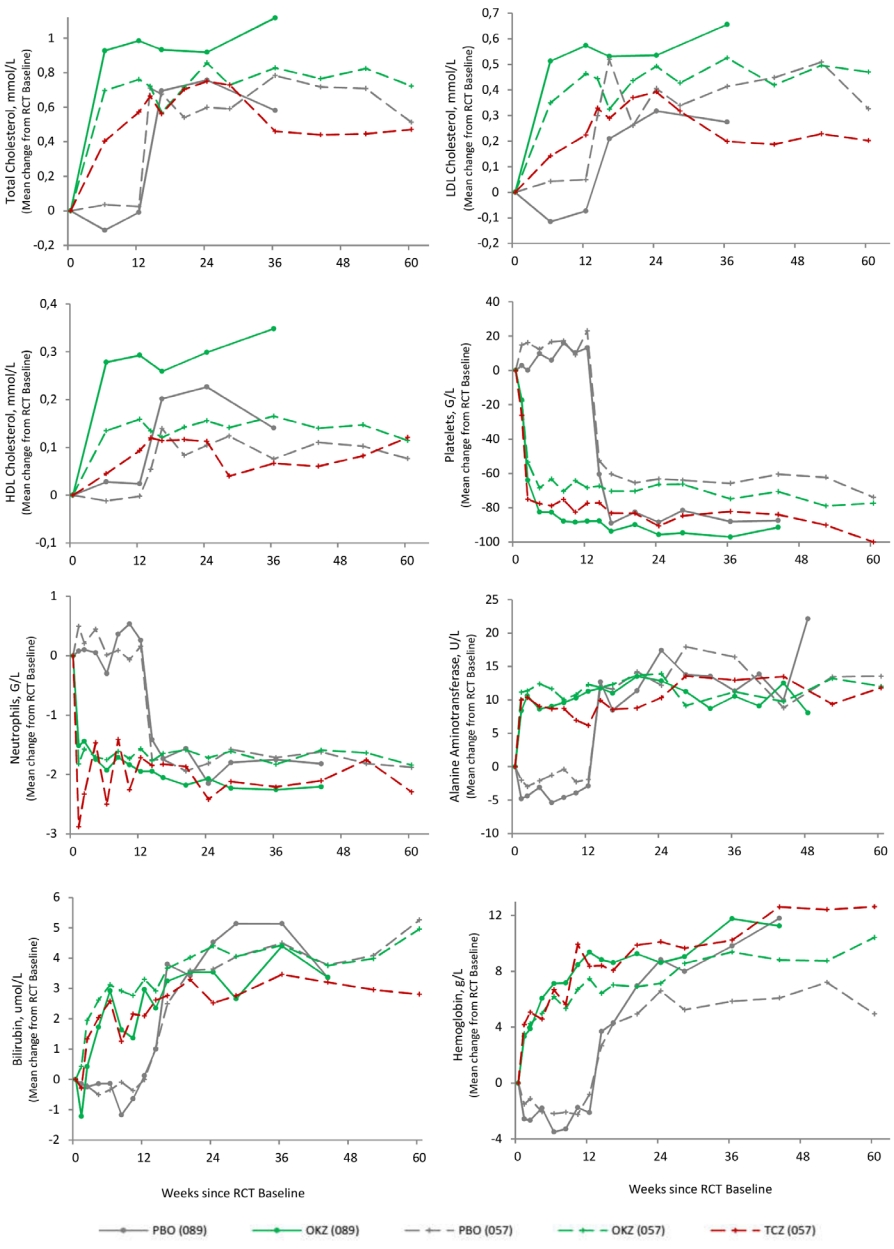

Figure 3. Blood biochemistry parameters' dynamics during RA057/RA089 clinical trials from RCTs baseline.
G, giga=10^9; 0 indicates baseline numbers that were within the normal range (hemoglobin mean baseline [standard deviation]) of hemoglobin numbers (g/L) were decreased: in RA0057 within the lower limit of norm -126,0(12,3) for OKZ, 129,3(13,3) for PBO and 124,2(9,9) for TCZ and in RA0089 below the lower limit of norm - 116,2(13,6) for OKZ and 119,5(15,0) for PBO.
RCT: randomized controlled trial; OKZ: olokizumab; PBO: placebo; TCZ: tocilizumab; SD: standard deviation.

viously failed anti-TNF therapies and thus may not be generalizable to the full RA population.

In conclusion, we present long-term safety, efficacy, and PRO data from 2 phase II RCT and OLE studies of OKZ. Our data showed that OKZ is generally well tolerated during long-term use with a safety profile similar to that of approved anti-IL-6 biologics with no unexpected safety findings. Clinical efficacy of OKZ seen during RCT phase of these studies is maintained during OLE, and improvements in PROs are consistent with other efficacy outcomes.

Ethics Committee Approval: Constituted independent ethics (IEC) or institutional review board (IRB) at each study center approved the definite documents such as clinical study protocol, study protocol amendment, written study subject information.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.C.G., E.K.; Design - M.C.G., E.K.; Supervision - M.C.G., P.D., R.F., Y.T., D.F., H.Y., T.T.; Data Collection and/or Processing - I.V.; Analysis and/or Interpretation - M.C.G., R.F., E.K., I.V.; Literature Search - E.K.; Writing Manuscript - M.C.G., P.D., R.F., D.F., E.K.; Critical Review - M.C.G., R.F., Y.T., H.Y., T.T.

Acknowledgements: The authors thank the investigators and patients who were part of this study, and acknowledge Sofia Kuzkina, MD, JSC "R-Pharm", Moscow, Russia, Saeed Fatenejad, MD, SFC Medica for editorial support and Thangavel Kaviarasu IQVIA, Bangalore, India for statistical analyses support.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: M.C.G. receives grants/research support and/or consulting fees from UCB Pharma, JSC "R-Pharm", Sanofi-Aventis, Roche, GlaxoSmithKline, BirdRock Bio. P.D. receives speakers' fees from Bristol-Myers Squibb, Eli Lilly, Pfizer, Sanofi. R.F. receives grants/research support from AbbVie, Acea, Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, MSD Serano, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB Pharma, and is consultant at AbbVie, Acea, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Pfizer, Sanofi-Aventis, Tahio, UCB Pharma. Y.T. receives speaker's fees, and/or honoraria from Daiichi-Sankyo, Astellas, Pfizer, Mitsubishi-Tanabe, Bristol-Myers, Chugai, YL Biologics, Eli Lilly, Sanofi, Janssen, UCB, and grants/research support from Mitsubishi-Tanabe, Takeda, Bristol-Myers, Chugai, Astellas, Abbvie, MSD, Daiichi-Sankyo, Pfizer, Kyowa- Kirin, Eisai, Ono. D.F. receives grant/research support from Abbott, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma; D.F. is at consultancy/advisory board in Abbott, Actelion, Amgen, Bristol-Myers Squibb, BiogenIdec, Janssen, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma; D.C. holds honoraria at Abbott, Actelion, Amgen, Bristol-Myers Squibb, BiogenIdec, Janssen, Gilead, NIH, Roche/Genentech. H.Y. is consultant at and receives grant/research support from UCB Pharma, Abbott, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda. T.K. is employee of IQVIA. I.V. is employee of JSC R-Pharm, with no R-Pharm stocks. E.K. is employee of JSC R-Pharm, with no R-Pharm stocks. T.T. is consultant at AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei; T.T. receives grant/research support from Abbott, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda, Teijin; T.T. is in speakers' bureau at UCB Pharma, Abbott, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda.

References

1. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76: 960-77. [Crossref]

2. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2016; 68: 1-26. [Crossref]
3. Tanaka Y, Martin Mola E. IL-6 targeting compared to TNF targeting in rheumatoid arthritis: Studies of olokizumab, sarilumab and sirukumab. Ann Rheum Dis 2014; 73: 1595-7. [Crossref]
4. Heijde D, Strand V, Tanaka Y, Keystone E, Kremer J, Zerbini CAF, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: Clinical efficacy, radiographic, and safety outcomes from a twenty-four-month, phase III study. Arthritis Rheumatol 2019; 71: 878-91. [Crossref]
5. Winthrop KL, Weinblatt ME, Bathon J, Burmester GR, Mease PJ, Crofford L, et al. Unmet need in rheumatology: Reports from the Targeted Therapies meeting 2019. Ann Rheum Dis 2020; 79: 88-93. [Crossref]
6. Shaw S, Bourne T, Meier C, Carrington B, Gelinas R, Henry A, et al. Discovery and characterization of olokizumab: A humanized antibody targeting interleukin-6 and neutralizing gp130-signaling. MAbs 2014; 6: 774-82. [Crossref]
7. Genovese MC, Fleischmann R, Furst D, Janssen N, Carter J, Dasgupta B, et al. Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: Outcomes of a randomised Phase IIb study. Ann Rheum Dis 2014; 73: 1607-15. [Crossref]
8. Takeuchi T, Tanaka Y, Yamanaka H, Amano K, Nagamine R, Park W, et al. Efficacy and safety of olokizumab in Asian patients with moderate-to-severe rheumatoid arthritis, previously exposed to anti-TNF therapy: Results from a randomized phase II trial. Mod Rheumatol 2016; 26: 15-23. [Crossref]
9. Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS, et al. The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24. [Crossref]
10. Knevel R, Schoels M, Huizinga TWJ, Aletaha D, Burmester GR, Combe B, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: A systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010; 69: 987-94. [Crossref]
11. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). Clin Exp Rheumatol 2005; 23: S14-8.
12. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980; 23: 137-45. [Crossref]
13. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: A review of the literature. Arthritis Res Ther 2016; 18: 251. [Crossref]
14. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis Care Res (Hoboken) 2011; 63 Suppl 11: S14-36. [Crossref]
15. Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of Euroqol--a generic health status instrument--in patients with rheumatoid arthritis. Economic and Health Outcomes Research Group. Br J Rheumatol 1994; 33: 655-62. [Crossref]
16. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199-208. [Crossref]
17. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S. Measuring fatigue in rheumatoid arthritis: A cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. Arthritis Care Res (Hoboken) 2010; 62: 1559-68. [Crossref]
18. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: The patient's perspective. J Rheumatol 1993; 20: 557-60.
19. Pope JE, Khanna D, Norrie D, Ouimet JM. The minimally important difference for the health assessment questionnaire in rheumatoid arthritis clinical practice is smaller than in randomized controlled trials. J Rheumatol 2009; 36: 254-9. [Crossref]
20. Dures EK, Hewlett SE, Cramp FA, Greenwood R, Nicklin JK, Urban M, et al. Reliability and sensitivity to change of the Bristol Rheumatoid Arthritis Fatigue scales. Rheumatology (Oxford) 2013; 52: 1832-9. [Crossref]
21. Krishnan E, Sokka T, Häkkinen A, Hubert H, Hannonen P. Normative values for the Health Assessment Questionnaire disability index: Benchmarking disability in the general population. Arthritis Rheum 2004; 50: 953-60. [Crossref]
22. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol 2015; 16: 448-57. [Crossref]
23. Srirangan S, Choy EH. The role of Interleukin 6 in the pathophysiology of rheumatoid arthritis. Ther Adv Musculoskelet Dis 2010; 2: 247-56. [Crossref]
24. Hashizume M, Mihara M. The roles of Interleukin-6 in the pathogenesis of rheumatoid arthritis. Arthritis 2011; 2011: 1-8. [Crossref]
25. Barton J. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence 2009; 3: 335-44. [Crossref]
26. Fleischmann R, Genovese MC, Lin Y, St John G, van der Heijde D, Wang S, et al. Long-term safety of sarilumab in rheumatoid arthritis: An integrated analysis with up to 7 years' follow-up. Rheumatology (Oxford) 2019; 59: 292-302. [Crossref]
27. Bird P, Peterfy C, Countryman P, Griffiths H, Barrett R, Youssef P, et al. AC-CUTE: An Open-Label Study to Evaluate Progression of Structural Joint Damage and Inflammation in Subjects with Moderate to Severe Rheumatoid Arthritis. Int J Rheumatol 2018; 2018: 1-9. [Crossref]
28. Choy E, Caporali R, Xavier R, Fautrel B, Sanmarti R, Bao M, et al. Subcutaneous tocilizumab in rheumatoid arthritis: Findings from the common-framework phase 4 study programme TOZURA conducted in 22 countries. Rheumatology (Oxford) 2018; 57: 499-507. [Crossref]
29. Ogata A, Amano K, Dobashi H, Inoo M, Ishii T, Kasama T, et al. Longterm safety and efficacy of subcutaneous tocilizumab monotherapy: Results from the 2-year open-label extension of the MUSASHI study. J Rheumatol 2015; 42: 799-809. [Crossref]
30. Ogata A, Tanaka Y, Ishii T, Kaneko M, Miwa H, Ohsawa S, et al. Long-term safety and efficacy of weekly subcutaneous tocilizumab monotherapy in patients with rheumatoid arthritis who had an inadequate response to subcutaneous tocilizumab every other week: Results from the open-label extension of the SHINOBI study. Mod Rheumatol 2019; 29: 767-74. [Crossref]
31. Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, et al. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: Safety, efficacy and radiographic outcomes. Rheumatology (Oxford) 2018; 57: 1423-31. [Crossref]
32. Kojima M, Kojima T, Suzuki S, Takahashi N, Funahashi K, Asai S, et al. Patient-reported outcomes as assessment tools and predictors of long-term prognosis: A 7-year follow-up study of patients with rheumatoid arthritis. Int J Rheum Dis 2017; 20: 1193-200. [Crossref]
33. Strand V, Lee EB, Fleischmann R, Alten RE, Koncz T, Zwillich SH, et al. Tofacitinib versus methotrexate in rheumatoid arthritis: Patient-reported outcomes from the randomised phase III ORAL Start trial. RMD Open 2016; 2: e000308. [Crossref]
34. Strand V, Gossec L, Proudfoot CWJ, Chen C-I, Reaney M, Guillonneau S, et al. Patient-reported outcomes from a randomized phase III trial of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis. Arthritis Res Ther 2018; 20: 129. [Crossref]