ONLINE SUPPLEMENTARY MATERIALS

(Adapted from the protocol)

SUPPLEMENTARY METHODS

Randomization and blinding

After eligibility had been confirmed, subjects were randomized in a 2:2:1 ratio by blinded study staff using the IWRS (an automated web randomization system). All subjects randomized to the placebo group were also randomized by blinded study staff using the IWRS in a 1:1 ratio to receive one of the 2 olokizumab (OKZ) treatment regimens starting at Week 16 and continuing for the remainder of the double-blind Treatment Period. The IWRS allocated the treatment group and assigned the study drug. 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.

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 C-reactive protein (CRP) and erythrocyte sedimentation rate (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 data and safety monitoring boar (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.

Criteria for evaluation, determination of sample size and selection of non-inferiority margin

Primary efficacy endpoint:

The primary efficacy endpoint was the ACR20 response at Week 12, where a responder was defined as any subject satisfying ACR20 criteria and remaining on randomized treatment and in the study at Week 12.

Secondary efficacy endpoints:

The secondary efficacy endpoints were:

- Percentage of subjects achieving low disease activity, defined as DAS28 (CRP) <3.2, and remaining on randomized treatment and in the study at Week 12
- Improvement of physical ability from baseline to Week 12, as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI)
- Percentage of subjects achieving an ACR50 response and remaining on randomized treatment and in the study at Week 12
- Percentage of subjects with Clinical Disease Activity Index (CDAI) ≤2.8 (remission) and remaining on randomized treatment and in the study at Week 12.

Other efficacy endpoints

Exploratory endpoints including proportion of subjects achieving an ACR20, ACR50, and ACR70 response and remaining on randomized treatment and in the study, assessed at all applicable time points; proportion of subjects with Simplified Disease Activity Index (SDAI)≤3.3 (remission) and remaining on randomized treatment and in the study, assessed at all applicable time points; proportion of subjects with CDAI ≤2.8 (remission) and remaining on randomized treatment and in the study, assessed at all other applicable time points; proportion of subjects with DAS28 DAS28[CRP]<3.2 and remaining on randomized treatment and in the study at all other applicable time points, etc.

Patient inclusion criteria

Subjects were enrolled in the study only if they 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 must have a diagnosis of adult-onset rheumatoid arthritis (RA) classified by ACR/EULAR 2010 revised classification criteria for RA [1] for at least 24 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. Treatment with oral, SC, or intramuscular methotrexate (MTX) for at least 12 weeks prior to Screening at a dose of 15 to 25 mg/week (or ≥10 mg/week if there is documented intolerance to higher doses)
    - The dose and means of administering MTX must have been stable for at least 6 weeks prior to Screening.
5. Subjects must be willing to take folic acid or equivalent throughout the study.
6. Subjects must have moderately to severely active RA disease as defined by all of the following:
    - ≥6 tender joints (68-joint count) at Screening and baseline; and
    - ≥6 swollen joints (66-joint count) at Screening and baseline; and
    - CRP above upper limit of normal (ULN) at Screening based on the central laboratory results
7. Subjects must have a documented inadequate response to treatment (i.e., tumor necrosis factor inhibitors (TNFi) failure) with ≥1 licensed TNFi following at least 12 weeks of therapy with that agent. Inadequate response to treatment is classified as either:
    - Primary failure: The absence of any documented clinically significant response; or
    - Secondary failure: Documented initial response with subsequent loss of that response or partial response

Exclusion criteria

Subjects who meet any of the following criteria were not 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 may 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 Janus kinases and spleen tyrosine kinase [SYK] inhibitors)
4. Prior treatment with cell-depleting therapies, including anti-CD20 agents or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, and anti-CD19), with the exception of rituximab, which was allowed with a washout period of 24 weeks prior to baseline (rituximab should not be 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)
5. Prior use of biologic disease-modifying antirheumatic drugs (bDMARDs) within the following windows prior to baseline (bDMARDs should not be 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):
    - 4 weeks for etanercept
    - 8 weeks for infliximab
    - 10 weeks for adalimumab, certolizumab, and golimumab
    - 12 weeks for abatacept
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 history of no response to hydroxychloroquine and sulfasalazine
9. Prior use of cDMARDs (other than MTX) within the following windows prior to baseline (cDMARDs were not to be 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):

- 4 weeks for sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penicillamine, minocycline, or doxycycline
- 12 weeks for leflunomide unless the subject has 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
- 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 is 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:
    - Creatinine level ≥1.5nmg/dL (132 µmol/L) for females or ≥2.0 mg/dL (177 µmol/L) for males
    - Alanine transaminase (ALT) or aspartate transaminase (AST) level ≥1.5 times ULN
    - Platelets $<100\times10^9$/L ($<100{,}000/mm^3$)
    - White blood cell count $<3.5\times10^9$/L
    - Neutrophil count $<2000\times10^6$/L ($<2000/mm^3$)
    - Hemoglobin level ≤80 g/L
    - 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 HBsAg, anti-HBc, or HCV Ab)

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

18. Subjects with human immunodeficiency virus infection

19. Subjects with:

    - Suspected or confirmed current active tuberculosis (TB) infection or a history of active TB infection.

    - 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.

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

        – 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 was not to be used); and

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

    - Positive 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 was to be excluded.

        – 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 could not be used); and
3. The subject was willing to complete the entire course of recommended LTBI therapy.

– 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 were 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 in situ of the cervix 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 cardio-vascular (CV) conditions:

- Uncompensated congestive heart failure, or class III or IV heart failure defined by the New York Heart Association classification [2]
- Untreated or resistant arterial hypertension Grade II-III (systolic blood pressure [BP] >160 mm Hg and/or diastolic BP >100 mm Hg)
- 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 would, in the Investigator's judgment, contraindicate subject participation in the clinical study, or clinically significant enough in the opinion of the Investigator to alter the disposition of the study treatment, or constitute 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, gastrointestinal (GI), endocrinological, dermatological, neurological, psychiatric, hematological [including bleeding disorder], or immunologic/immunodeficiency disorder[s]) that would, in the Investigator's judgment, contraindicate subject participation in the clinical study, or clinically significant enough in the opinion of the Investigator to alter the disposition of the study treatment, or constitute 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 a 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 might 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, currently lactating, had lactated within the last 12 weeks, or who were planning to become pregnant during the study or within 6 months of the last dose of study treatment
31. Female subjects of childbearing potential (unless permanent cessation of menstrual periods, determined retrospectively after a woman has 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 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 drug

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 drug.

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 drug
  - In the case of oophorectomy alone, only when the reproductive status of the woman has 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 should 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 to any component of the rescue therapy
34. History of severe allergic or anaphylactic reactions to human, humanized, or mural 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 may increase potential risk associated with study participation and administration of investigational products, or that

may affect study results interpretation and, as per the Investigator's judgment, make the subject ineligible

Premature subject study withdrawal

All subjects were free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment.

If premature withdrawal occurred for any reason, the Investigator made every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the source documents and appropriate electronic case report form (eCRF).

Subjects were completely withdrawn from study treatment and all assessments in the following cases:

- Withdrawal of informed consent
- Death of subject
- Subject lost to follow-up

Premature subject treatment withdrawal

If a subject who did not meet enrollment criteria was inadvertently enrolled, study treatment was immediately and permanently discontinued.

If, in the opinion of the Investigator, a subject was consistently noncompliant with the protocol study procedures, use of concomitant medications, or dosing with the study treatment, a case-by-case review was conducted by the Sponsor and noncompliant subjects could be discontinued from study treatment.

If the Investigator judged that the subject's health was deteriorating or not improving, the Investigator could elect to discontinue the subject from the study treatment. Appropriate standard of care, at the discretion of the Investigator, was to be initiated.

In addition to the above, study treatment was permanently discontinued in the following circumstances:

- Investigator decided that the subject should be discontinued from study treatment. If this decision was made because of an intolerable adverse effects (AE) or a clinically significant laboratory value, the study treatment was to be discontinued, appropriate measures are to be taken, and the Sponsor or Sponsor`s designee was to be notified.
- Subject was unwilling to continue the study treatment. If the subject discontinued from the study treatment, the Investigator was to inquire about the reason for discontinuing.

- Subject presented with any of the following elevated liver function tests:
  - Alanine transaminase (ALT) or aspartate transaminase (AST) elevations >8× ULN at any time, regardless of total bilirubin or accompanying symptoms
  - ALT or AST >5× ULN for ≥2 weeks regardless of total bilirubin or accompanying symptoms
  - ALT or AST elevations >3× ULN and total bilirubin value >2× ULN
  - ALT or AST elevations >3× ULN accompanied by symptoms consistent with hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash)
- Subject presented with any of the following laboratory abnormalities:
  - Absolute neutrophil count $<500\times10^6$/L (<500 /mm^3)
  - Two sequential lymphocyte counts $<500\times10^6$/L (<500 /mm^3)
  - Platelet count $<50\times10^9$/L (<50,000 /mm^3 or $<50{,}000\times10^6$/L)
  - Two sequential hemoglobin values ≤8.0 g/dL (80 g/L) and decreased ≥2 g/dL (20 g/L) below Screening value
  - Creatinine value >2× ULN
- Subject had confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
- The Sponsor, a regulatory agency, or an ethical committee stopped the study for any reason.
- Administration of a live vaccine during the study.
- Subject had a GI perforation.
- Subject had a severe or life-threatening infection that required hospitalization (which is also an SAE).
  - Confirmed active TB was an SAE, was to be recorded on the relevant AE pages of the eCRF, and periodic follow-up reports were to be completed according to protocol requirements (i.e., through 22 weeks of safety follow-up) until the TB infection resolved.

Prior and concomitant treatments

All subjects received background treatment with MTX. 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 was not to be taken on the same day as MTX.

Specific treatments prohibited prior to (as applicable) and during the course of the study are 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. All medications/treatments received within 4 weeks prior to the Screening Visit were also 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 were recorded too.

Table S1 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 at Week 14 as described below. • Prior use of cDMARDs other than MTX within the following windows prior to baseline was exclusionary (cDMARDs were not to be 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, with the following exception: o Subjects who discontinued TNFi therapy due to a reason other than lack of efficacy were allowed to enter the study (TNFi therapy was not to be 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: - 4 weeks for etanercept - 8 weeks for infliximab - 10 weeks for adalimumab, certolizumab, and golimumab
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

Table S1 Prohibited medications

Treatment	Restriction
	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 were performed. The injection was not to exceed 40 mg methylprednisolone or equivalent cumulative dose. Injected joints must 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 S table doses of NSAIDs were permitted during the study if the subject had received stable doses for ≥2 weeks prior to baseline. Doses of NSAIDs must 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 required discontinuation of the NSAID, an alternative NSAID could be initiated per the local label (if not contraindicated). • Aspirin use at daily doses up to 325 mg was permitted if indicated for CV protection. At this dose, aspirin was not considered an NSAID.
Analgesics	• Analgesics, including opioids, were prohibited during the entire study with the following exception: o Paracetamol/acetaminophen: Maximum 2000 mg per day (maximum 1000 mg per dose). Paracetamol/acetaminophen were 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 is exclusionary.
Vaccination	• Live vaccinations were prohibited during the entire study and their use within 12 weeks prior to baseline is 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 drugs; 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

Allowed medication included, but was not limited to:

- Inhaled corticosteroids
- Topical corticosteroids
- Oral corticosteroids

  - Doses of ≤10 mg/day of prednisone or equivalent were permitted if the dose was not 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 were performed. The cumulative dose for both injections could not exceed 40 mg methylprednisolone or equivalent. Joints treated with IA corticosteroids must be rated with their pre-injection status for the remainder of the study and 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 changed 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 were 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 non-responders defined as all subjects who do not improve by at least 20% in both SJC and TJC (66-68 joint assessment). Standalone Independent Joint Assessment was performed at Week 14 for this purpose. Non-responders 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

Non-responders 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) should be made according to local practice, and the assigned rescue medication regimen should be maintained throughout the study.

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

Demography and disease characteristic

Table S2. The numbers of randomized patients from each country (ITT population)

Country, n (%)	OKZ 64 mg q2w N=138	OKZ 64 mg q4w N=161	PBO N=69	Total N=368
Argentina	11 (8.0)	14 (8.7)	3 (4.3)	28 (7.6)
Brazil	11 (8.0)	8 (5.0)	5 (7.2)	24 (6.5)
Colombia	5 (3.6)	3 (1.9)	5 (7.2)	13 (3.5)
Czech Republic	13 (9.4)	17 (10.6)	6 (8.7)	36 (9.8)
Germany	1 (0.7)	3 (1.9)	0	4 (1.1)
Hungary	10 (7.2)	8 (5.0)	6 (8.7)	24 (6.5)
South Korea	2 (1.4)	1 (0.6)	1 (1.4)	4 (1.1)
Mexico	28 (20.3)	27 (16.8)	18 (26.1)	73 (19.8)
Poland	5 (3.6)	5 (3.1)	3 (4.3)	13 (3.5)
Russia	8 (5.8)	12 (7.5)	1 (1.4)	21 (5.7)
United States	44 (31.9)	63 (39.1)	21 (30.4)	128 (34.8)
Region				
Western	68 (49.3)	91 (56.5)	33 (47.8)	192 (52.2)
Latin America	55 (39.9)	52 (32.3)	31 (44.9)	138 (37.5)
Rest of the World	15 (10.9)	18 (11.2)	5 (7.2)	38 (10.3)

Note: Region is defined as follows: Western (United States, Czech Republic, Hungary, Germany), Latin America (Argentina, Brazil, Columbia, Mexico), Rest of World (Russia, Poland, South Korea)
Abbreviations: ITT, intention-to-treat; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w , every 4 weeks; n, number of subjects; %, percentage of subjects calculated relative to the total number of subjects in the population.

Table S3. Number of previous TNF by treatment group (ITT population)

Number of previous TNF, n (%)	OKZ 64 mg q2w N=139	OKZ 64 mg q4w N=160	PBO N=69
1	112 (80.6)	127 (79.4)	52 (75.4)
2	19 (13.7)	29 (18.1)	10 (14.5)
3	4 (2.9)	2 (1.3)	4 (5.8)
4	1 (0.7)	0	0

Abbreviations: ITT, intention-to-treat; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w , every 4 weeks; n, number of subjects; %, percentage of subjects calculated relative to the total number of subjects in the population.

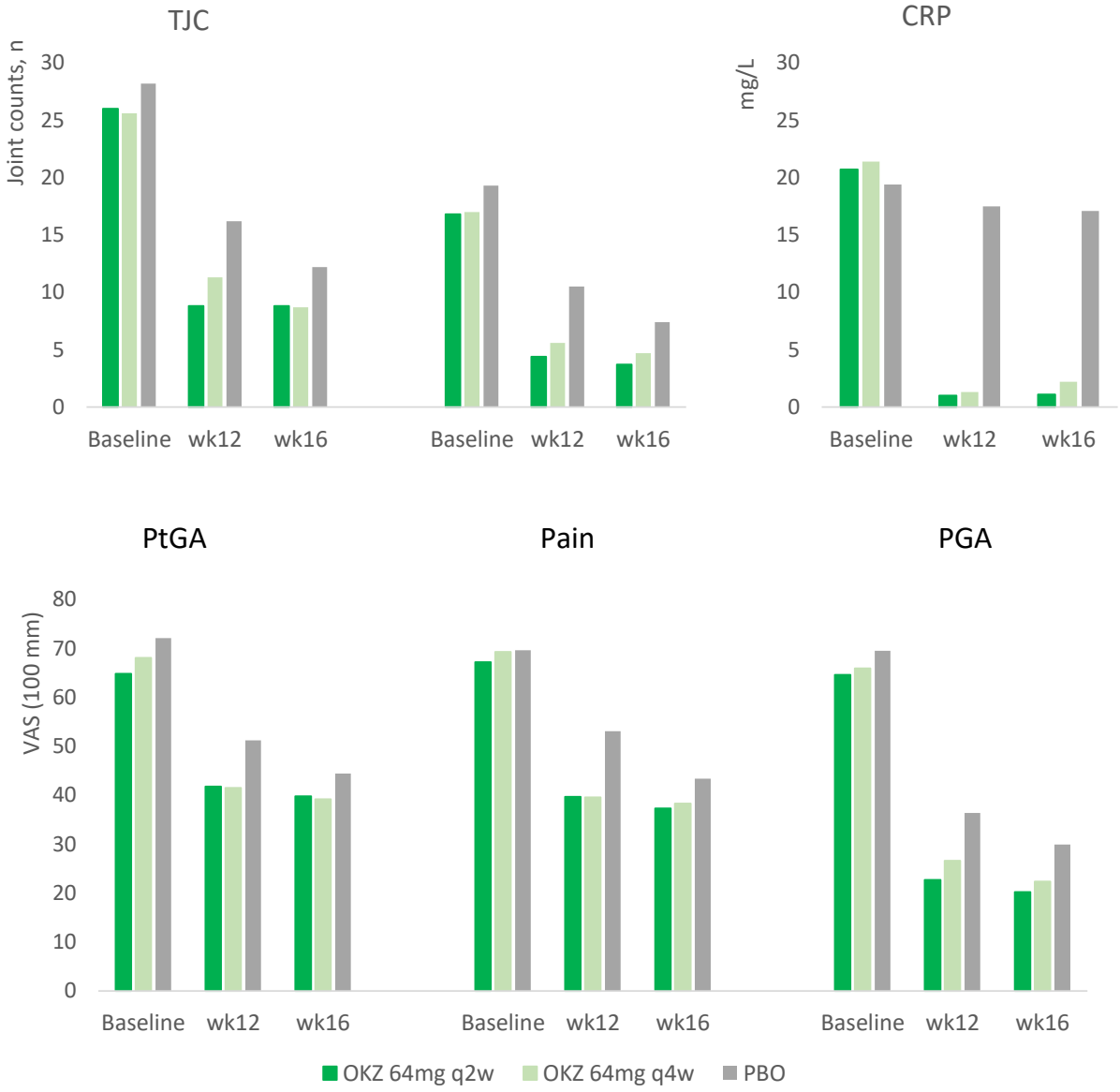
Table S4. Number of previous TNF by duration (ITT population)

Duration (in days) of previous TNFi	ADA	CZP	ETC	GOM	INX
N	158	30	175	22	69
≥ 6 months, n (%)	131 (82.9)	24 (80.0)	152 (86.9)	18 (81.8)	58 (84.1)
< 6 months, n (%)	27 (17.1)	6 (20.0)	23 (13.1)	4 (18.2)	11 (15.9)

Abbreviations: ADA, adalimumab; CER, certolizumab/certolizumab pegol; ETC, etanercept; GOM, golimumab; ITT, intention-to-treat; INX, infliximab; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w , every 4 weeks; SD, standard deviation; ; n, number of subjects; %, percentage of subjects calculated relative to the total number of subjects in the population.

Additional efficacy

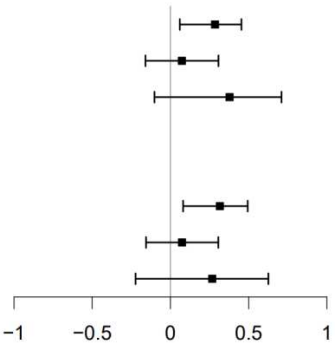
Figure S1. Core components of ACR response criteria (mean numbers) during the double-blind treatment period (ITT population)



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

Figure S2. ACR20 response rates for olokizumab relative to placebo at week 12 by region (ITT population)

Region	OKZ Nx / n (%)	Placebo (N=69) Nx / n (%)	Risk difference (97.5% CI)
OKZ 64 mg q4w (N=161)			
Western	48 / 91 (52.7)	8 / 33 (24.2)	0.285 (0.060, 0.454)
Latin America	34 / 52 (65.4)	18 / 31 (58.1)	0.073 (−0.160, 0.307)
Rest of the World	14 / 18 (77.8)	2 / 5 (40.0)	0.378 (−0.102, 0.710)
OKZ 64 mg q2w (N=138)			
Western	38 / 68 (55.9)	8 / 33 (24.2)	0.316 (0.081, 0.494)
Latin America	36 / 55 (65.5)	18 / 31 (58.1)	0.074 (−0.156, 0.306)
Rest of the World	10 / 15 (66.7)	2 / 5 (40.0)	0.267 (−0.223, 0.626)



Note: Region is defined as follows: Western (United States, Czech Republic, Hungary, Germany), Latin America (Argentina, Brazil, Columbia, Mexico), Rest of World (Russia, Poland, South Korea);

Abbreviations: ACR20, American college of rheumatology 20%; ITT, intent-to-treat; OKZ, olokizumab; N, number of subjects in the analysis population; Nx, number of subjects contributing to the analysis at the corresponding time point; n, umber of responders; %, for Nx the percentage of subjects is calculated relative to the total number of subjects in the population. For n the percentage is calculated relative to Nx.

Additional safety

Table S5. Incidence of AESI up to week 16 (safety population)

System organ class, n (%)	Any OKZ q2w N=171	Any OKZ q4w N=186
Patients with ≥ 1 AESI	86 (50.3)	78 (41.9)
Infections	54 (31.6)	48 (25.8)
Opportunistic infections	1 (0.6%	0
Malignancies	2 (1.2)	0
Basal cell carcinomas	0	0
Elevation of blood lipids	15 (8.8)	16 (8.6)
Systemic injection and hypersensitivity reactions	17 (9.9)	13 (7.0)
Anaphylactic reactions	0	1 (0.5)
Gastrointestinal perforation	0	0
Neutro-, thrombocyto-, leukocyto-, and pancytopenia	10 (5.8)	7 (3.8)
Potential hepatotoxicity	9 (5.3)	7 (4.4)
Injection site reactions	7 (4.1)	14 (7.5)
Demyelination in peripheral or central nervous system	0	0
Autoimmune disorders	1 (0.6)	2 (1.1)

Notes: %, percentage of patients calculated relative to the total number of patients in the treatment arm. MedDRA (Medical Dictionary for Regulatory Activities) Version 21.1 was used to code AEs. A TEAE was defined as an AE that first occurred or worsened in severity after the first dose of the study treatment; potential hepatotoxicity was defined as laboratory results for ALT>3×ULN (or AST in case ALT results were unavailable) and reported by investigators.
Any OKZ group, subjects randomized to receive appropriate OKZ dosage at baseline plus subjects re-randomized starting at week 16 (after receiving placebo); only those assessments or events that occurred after administration of OKZ was included.
Abbreviations: AESI, adverse events of special interest; n, number of subjects; %, percentage of subjects calculated relative to the total number of subjects in the population.

Table S6. Incidence of serious treatment-emergent adverse events by system organ class and preferred term in the entire study (safety population)

System Organ Class/Preferred Term, n (%)	**Any OKZ q2w** N=171	**Any OKZ q4w** N=186
Patients with ≥ 1 TESAE	**12 (7.0)**	**6 (3.2)**
Cardiac disorders/sinus bradycardia	**0**	**1 (0.5)**
Gastrointestinal disorders/gastrointestinal disorders	**0**	**1 (0.5)**
Hepatobiliary disorders/cholecystitis	1 (0.6)	0
Immune system disorders/anaphylactic reaction	**0**	**1 (0.5)**
Infections and infestations/	**2 (1.2)**	**2 (1.1)**
Cellulitis	1 (0.6)	1 (0.5)
Pilonidal cyst	1 (0.6)	0
Sepsis	0	1 (0.5)
Pneumonia	1 (0.6)	0
Injury, poisoning and procedural complications	**1 (0.6)**	**0**
Hip fracture	1 (0.6)	0
Ulna fracture	1 (0.6)	0
I**nvestigations/**	**2 (1.2)**	**1 (0.5)**
Alanine aminotransferase increased	0	1 (0.5)
Aspartate aminotransferase increased	1 (0.6)	0
Transaminases increased	1 (0.6)	0
Musculoskeletal and connective tissue disorders/	**3 (1.8)**	**0**
Intervertebral disc protrusion	1 (0.6)	0
Musculoskeletal chest pain	1 (0.6)	0
Osteoarthritis	1 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/invasive ductal breast carcinoma	**1 (0.6)**	**0**
Psychiatric disorders/anxiety	**1 (0.6)**	**0**
Renal and urinary disorders/renal failure	0	**1 (0.5)**
Vascular disorders/hypertensive crisis	**1 (0.6)**	**0**

Notes: n, number of patients; %, percentage of patients calculated relative to the total number of patients in the treatment arm. MedDRA (Medical Dictionary for Regulatory Activities) Version 21.1 was used to code AEs. A TESAE is defined as an serious AE that first occurred or worsened in severity after the first dose of the study treatment; any OKZ, who has received at least 1 dose of OKZ.

Abbreviations: OKZ, olokizumab; pts, patients; TESAE, treatment-emergent serious adverse event; q2w, every 2 week; q4w, every 4 weeks

Table S7. Incidence of treatment-emergent adverse events by system organ class in the entire study (safety population)

System Organ Class, n (%) Preferred terms	**Any OKZ q2w** N=171	**Any OKZ q4w** N=186	**PBO** N=69
Patients with ≥ 1 TEAE	**110 (64.3)**	**111 (59.7)**	**35 (50.7)**
Blood and lymphatic system disorders	11 (6.4)	9 (4.8)	5(7.2)
Cardiac disorders	2 (1.2)	3 (1.6)	1(1.4)
Ear and labyrinth disorders	1 (0.6)	2 (1.1)	0
Eye disorders	3 (1.8)	6 (3.2)	0
Gastrointestinal disorders	24 (14.0)	19 (10.2)	6(8.7)
General disorders and administration site conditions	8 (4.7)	18 (9.7)	3(4.3)
Hepatobiliary disorders	9 (5.3)	6 (3.2)	1(1.4)
Immune system disorders	1 (0.6)	1(0.5)	0
Infections and infestations	54 (31.6)	48 (25.8)	18 (26.1)
Injury, poisoning and procedural complications	5 (2.9)	12 (6.5)	1(1.4)
Investigations	28 (16.4)	27 (14.5)	4(5.8)
Metabolism and nutrition disorders	13 (7.6)	14 (7.5)	1(1.4)
Musculoskeletal and connective tissue disorders	13 (7.6)	11 (5.9)	5(7.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2)	2(1.1)	1 (1.4)
Nervous system disorders	6 (3.5)	6 (3.2)	2 (2.9)
Psychiatric disorders	3 (1.8)	0	0
Renal and urinary disorders	0	6 (3.2)	0
Reproductive system and breast disorders	3 (1.8)	1 (0.5)	1(1.4)
Respiratory, thoracic and mediastinal disorders	4 (2.3)	5 (2.7)	0
Skin and subcutaneous tissue disorders	14 (8.2)	13 (7.0)	1(1.4)
Vascular disorders	7 (4.1)	5 (2.7)	3(4.3)
TEAE, leading to study treatment discontinuation*	**7 (4.1)**	**10 (5.4)**	**1(1.4)**
TEAE, leading to death	**0**	**0**	**0**

Notes: n, number of patients; %, percentage of patients calculated relative to the total number of patients in the treatment arm. MedDRA (Medical Dictionary for Regulatory Activities) Version 21.1 was used to code AEs. A TEAE is defined as an AE that first occurred or worsened in severity after the first dose of the study treatment;

* TEAE, leading to study treatment discontinuation by organ class/*preferred term* were:

OKZ q2w arm: 2pts with infections and infestations/*cellulitis* (1pt), *herpes zoster* (1pt); 3pts with investigations/*aspartate aminotransferase increased* (1pt*), transaminases increased* (1pt), *neutrophil count decreased* (1pt); 1pt with neoplasms benign, malignant and unspecified (incl cysts and polyps/ *squamous cell carcinoma*; 1pt with blood and lymphatic system disorders/*thrombocytopenia*;

OKZ q4w arm: 4pts with infections and infestations/*cellulitis* (1pt), *abscess limb* (1pt), *pneumonia* (1pt), *sinusitis* (1pt); 3pts with investigations/ a*lanine aminotransferase increased increased* (2pts), *lymphocyte count decreased* (1pt); 1pt with immune system disorders/*anaphylactic reaction*;1pt with injury, poisoning and procedural complication/*toxicity to various agents*; and 1pt with skin and subcutaneous tissue disorders/*blister*;

PBO arm: 1pt with neoplasms benign, malignant and unspecified (incl cysts and polyps)/*invasive ductal breast carcinoma*.

Abbreviations: OKZ, olokizumab; pts, patients; TEAE, treatment-emergent adverse event; q2w, every 2 week; q4w, every 4 weeks

Table S8. Patients with selected hematology assessments outside of the normal range (safety population)

Patients with			OKZ 64 mg q2w, N=139	OKZ 64 mg q4w, N=160	PBO, N=69
WBC count < 4000/mm^3 (or < 4 ·10^9/L)	BL	Nx(%)	139 (100.0)	160 (100.0)	69 (100.0)
		n(%)	**3 (2.2)**	**1 (0.6)**	**0 (0.0)**
	Wk 12	Nx(%)	119 (85.6)	132 (82.5)	60 (87.0)
		n(%)	**8 (6.7)**	**4 (3.0)**	**0 (0.0)**
	Wk 16	Nx(%)	119 (85.6)	129 (80.6)	53 (76.8)
		n(%)	**7 (5.9)**	**5 (3.9)**	**0 (0.0)**
ANC count < 1500/mm^3 (or < 1.5 ·10^9/L)	BL	Nx(%)	139 (100.0)	160 (100.0)	69 (100.0)
		n(%)	0 (0.0)	0 (0.0)	0 (0.0)
	Wk 12	Nx(%)	118 (84.9)	132 (82.5)	60 (87.0)
		n(%)	**2 (1.7)**	**3 (2.3)**	**0 (0.0)**
	Wk 16	Nx(%)	119 (85.6)	127 (79.4)	53 (76.8)
		n(%)	**1 (0.8)**	**1 (0.8)**	**0 (0.0)**
ALC count < 500/mm^3 (or < 0.5 ·10^9/L)	BL	Nx(%)	139 (100.0)	160 (100.0)	69 (100.0)
		n(%)	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**
	Wk 12	Nx(%)	118 (84.9)	132 (82.5)	60 (87.0)
		n(%)	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**
	Wk 16	Nx(%)	119 (85.6)	127 (79.4)	53 (76.8)
		n(%)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

Notes: ANC < 1000/mm^3 (or < 1.0 ·10^9/L) and Hemoglobin ≤80 g/L no observations; N, number of patients in the arm; Nx(%), number and percent of the patients with non-missing results; n(%), number and percent of the patients with abnormal parameters; %, percentage of patients with non-missing results is calculated relative to the total number of patients in the population, whilst all other percentages are calculated relative to the number of patients with non-missing results at a given visit

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BL, baseline; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; WBC, white blood cells; Wk, week.

Table S9. Patients with selected chemistry assessments outside of the normal range (safety population)

Patients with		**OKZ 64 mg q2w, N=139**	**OKZ 64 mg q4w, N=160**	**PBO, N=69**
ALT, n(%) BL	Nx	139 (100.0)	160 (100.0)	69 (100.0)
	ALT >1x ULN to ≤ 3x ULN	17 (12.2)	12 (7.5)	6 (8.7)
	>3x ULN to ≤ 5x ULN	1 (0.7)	0	0
	> 5x ULN	1 (0.7)	0	0
ALT, n(%) Post-BL	Nx	138 (99.3)	160 (100.0)	67 (97.1)
	ALT >1x ULN to ≤ 3x ULN	84 (60.9)	75 (46.9)	17 (25.4)
	>3x ULN to ≤ 5x ULN	8 (5.8)	11 (6.9)	0
	> 5x ULN	4 (2.9)	5 (3.1)	0
Bilirubin, n(%) BL	Nx	139 (100.0)	160 (100.0)	69 (100.0)
	> 2x ULN	0	0	0
Bilirubin, n(%) Post-BL	Nx	138 (99.3)	160(100.0)	67 (97.1)
	> 2x ULN	0	1 (0.6)	0
	Concomitant elevations	0	0	0
Cholesterol, n(%) BL	Nx	138 (99.3)	155 (96.9)	69 (100.0)
	High	47 (34.1)	46 (29.7)	18 (26.1)
Cholesterol, n(%) Post-BL	Nx	137 (98.6)	159 (99.4)	66 (95.7)
	High	106 (77.4)	120 (75.5)	26 (39.4)
Cholesterol shifts from normal to high	Wk 12, n(%)	40 (32.0)	45 (33.8)	7 (11.5)
	Mean change[1],(SD)	1.25 (0.44)	1.20 (0.67)	0.78 (0.59)
	Wk 16, n(%)	43 (35.0)	37 (28.5)	3 (5.7)
	Mean change[1],(SD)	1.36 (0.70)	1.15 (0.57)	1.53 (1.65)
LDL Cholesterol, n(%) BL	Nx	138 (99.3)	155 (96.9)	69 (100.0)
	High	24 (17.4)	27 (17.4)	9 (13.0)
LDL Cholesterol, n(%) Post-BL	Nx	137 (98.6)	159 (99.4)	66 (95.7)
	High	85 (62.0)	82 (51.6)	17 (25.8)
LDL Cholesterol shifts from normal to high	Wk 12, n(%)	27 (21.6)	27 (20.3)	3 (4.9)
	Mean change[1],(SD)	0.98 (0.40)	1.07 (0.49)	0.72 (0.25)
	Wk 16, n(%)	32 (26.0)	18 (13.8)	3 (5.7)
	Mean change[1],(SD)	1.23 (0.59)	1.00 (0.54)	1.03 (0.89)

Notes: 1, mmol/L; ALT ULN = 33 U/L for female and =41 U/L for male; bilirubin ULN total = 21 µmol/l , direct = 5 µmol/l, bilirubin indirect =17 µmol/l; N, number of patients in the population; Nx(%), number and percent of the patients with non-missing results; n(%), number and percent of the patients with abnormal parameters; %, percentage of patients with non-missing results is calculated relative to the total number of patients in the population, whilst all other percentages are calculated relative to the number of patients with non-missing results at a given visit

Abbreviations: ALT, alanine aminotransferase; BL, baseline; LDL, low density lipoproteins; OKZ, olokizumab; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation; ULN, upper limit of normal; Wk, week

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