Clinical Study Protocol

Protocol Title:	**A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Inadequately Controlled by Methotrexate Therapy**
Protocol Number:	**CL04041022: Clinical Rheumatoid Arthritis Development for Olokizumab (CREDO) 1**
Date of Protocol:	**30 March 2018**
Version of Protocol:	**Amendment 1.1 local version for Russia and Belarus**
Product:	**Olokizumab (CDP6038; L04041)**
IND No:	**104933**
EudraCT No:	**2014-004719-36**
Study Phase:	**III**
Sponsor:	**R-Pharm** **19-1, Berzarina Street, Moscow** **Russian Federation 123154**

Signatures

PROTOCOL TITLE: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Inadequately Controlled by Methotrexate Therapy

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| **Mikhail Samsonov** | **Signature** | **Date** |
| **Chief Medical Officer** | | |

Investigator Signature Page

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This protocol is a confidential communication of R-Pharm. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from R-Pharm.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed copy to R-Pharm's designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

EMERGENCY CONTACTS

24-hour emergency medical contact	+1 973-659-6677 +1 570-819-8565 (alternate number)
SAE reporting	All SAEs should be reported via the EDC system by completing the relevant pages of the eCRF. In the event that the EDC system is not functioning, SAEs must be reported to the following email addresses: QLS_Olokizumab@iqvia.com QLS_Olokizumab@quintiles.com

Abbreviations: eCRF = electronic Case Report Form; EDC = Electronic Data Capture; SAE = Serious Adverse Event.

SYNOPSIS

Name of Sponsor	R-Pharm	
Name of Finished Product	Olokizumab	
Name of Active Ingredient	Olokizumab (CDP6038; L04041)	
Title of Study:	A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Inadequately Controlled by Methotrexate Therapy	
Protocol No:	CL04041022: Clinical Rheumatoid Arthritis Development for Olokizumab (CREDO) 1	
Investigators:	A total of approximately 50 Investigators will be involved in the conduct of this study.	
Study sites:	The study will be conducted at approximately 50 sites across 4 countries globally, which may include Russia, Belarus, Turkey, and Bulgaria.	
Study duration:	Screening: 4 weeks Treatment Period: 24 weeks Safety Follow-Up: 20 weeks	Phase: III

Objectives:

Primary:

The primary objective of this study is to evaluate the efficacy of olokizumab (OKZ) 64 mg administered subcutaneously (SC) once every 2 weeks (q2w) or once every 4 weeks (q4w) relative to placebo in subjects with moderately to severely active rheumatoid arthritis (RA) inadequately controlled by methotrexate (MTX) therapy.

Secondary:

- To evaluate the efficacy of OKZ over time.
- To compare the physical function and quality of life of subjects receiving OKZ relative to placebo.
- To characterize population pharmacokinetics (PK) of OKZ and individual drug exposures.
- To assess the safety and tolerability of OKZ.

Criteria for Evaluation:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the American College of Rheumatology 20% (ACR20) response at Week 12, where a responder is defined as any subject satisfying ACR20 criteria and remaining on randomized treatment and in the study at Week 12. This endpoint will serve to demonstrate that the efficacy of OKZ is superior to placebo.

Secondary Efficacy Endpoints:

The following secondary endpoints will be evaluated:

- Percentage of subjects achieving low disease activity, defined as Disease Activity Score 28-joint count (DAS28) C-reactive protein (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 American College of Rheumatology 50% (ACR50) response and remaining on randomized treatment and in the study at Week 24

- Percentage of subjects with Clinical Disease Activity Index (CDAI) ≤2.8 (remission) and remaining on randomized treatment and in the study at Week 24

Other Efficacy Endpoints:

The following additional efficacy endpoints will be used to compare OKZ with placebo:

- Proportion of subjects achieving an ACR20, ACR50, and American College of Rheumatology 70% (ACR70) response and remaining on randomized treatment and in the study, assessed at all other 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 low disease activity (based on DAS28 [CRP] <3.2) and remaining on randomized treatment and in the study, assessed at all other applicable time points
- Proportion of subjects with improvement from baseline in HAQ-DI score ≥0.22 and remaining on randomized treatment and in the study, assessed at all applicable time points
- Change from baseline over time in DAS28 (CRP)
- Change from baseline to Weeks 12 and 24 in DAS28 erythrocyte sedimentation rate (ESR)
- Change from baseline to all other applicable time points in the measure of physical ability (HAQ-DI)
- Change from baseline to Weeks 12 and 24 in the scores for the following patient-reported outcome (PRO) measures:
  - Short Form-36 (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) total scores
  - European Quality of Life-5 Dimensions (EQ-5D)
  - Work Productivity Survey-Rheumatoid Arthritis (WPS-RA)
  - Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue)
- Change from baseline to all applicable time points in SDAI and CDAI
- Proportion of subjects with moderate to good responses for European League Against Rheumatism (EULAR) based on DAS28 (CRP) and remaining on randomized treatment and in the study, assessed at all applicable time points, where a moderate response is defined as either DAS28 (CRP) ≤5.1 with an improvement from baseline in DAS28 (CRP) >0.6 and ≤1.2, or DAS28 (CRP) >3.2 with an improvement from baseline in DAS28 (CRP) >1.2, and a good response is defined as DAS28 (CRP) ≤3.2 with an improvement from baseline in DAS28 (CRP) >1.2
- Change from baseline to all time points in the components of the American College of Rheumatology (ACR) response criteria

Pharmacokinetic Endpoints:

Olokizumab in plasma will be assessed as follows:

- All subjects: Blood samples for measurement of OKZ concentrations will be collected at each time a blood sample is taken for the determination of antidrug antibodies (ADAs) (ADA/PK matched subjects), with the exception of the final Safety Follow-Up Visit. However, OKZ concentrations will only be analyzed for subjects who have a confirmed positive ADA response in any of the postdose samples.
- PK subpopulation: In approximately one third (33%) of consenting subjects, OKZ concentrations will be collected periodically throughout the study at scheduled visits.
- Sample-rich PK subpopulation: at least 42 subjects in the PK subpopulation will be consented with an additional informed consent form (ICF) and serial blood samples will be collected following the first dose of study treatment (Week 0) and over a 4-week period at steady state (Weeks 20 through 24) to

reach appropriate number of the enrolled subjects for further analysis of PK parameters. Olokizumab PK parameters will be determined in subjects randomized to OKZ following single (Week 0) and multiple dose (Week 20) administration, as appropriate. The Interactive Web Response System (IWRS) will be constructed to select consenting subjects to be included in the PK subpopulation in a blinded fashion based on the treatment group to which they are randomized. The PK parameters assessed will include, but not be limited to, maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration-time curve over the dosing interval ($AUC_{[0\text{-}tau]}$), apparent systemic clearance (CL/F), and accumulation ratios (R_{ac}) for Cmax and $AUC_{(0\text{-}tau)}$.

Pharmacokinetic/Pharmacodynamic (PD) Correlations:

The PK/PD and immunogenicity of OKZ will be assessed by:

- Characterizing the dose/exposure-response relationships related to efficacy endpoints (e.g., ACR20 response) and identifying potential factors that may impact the efficacy endpoints.
- Characterizing the dose/exposure-response relationships related to safety endpoints (e.g., lipids and neutrophils) and identifying potential factors that may impact the safety endpoints.
- Evaluating the impact of ADAs on subject safety, efficacy, and PK of OKZ.

Exploratory Endpoints:

- Exploratory pharmacogenetic (PG) assessments (in subjects who sign the separate PG ICF only) to examine whether individual genetic variation in genes relating to drug metabolism, RA, and the drug target pathway confers a differential response to OKZ.
- Exploratory biomarker assessments aiming to identify potential markers that are associated with treatment response to OKZ, correlated with the severity or progression of RA, or are cardiovascular (CV) surrogate biomarkers.

Safety Endpoints:

The safety of OKZ will be assessed by:

- The nature, incidence, severity, and outcome of adverse events (AEs), including serious adverse events (SAEs) and adverse events of special interest (AESIs).
- Proportions of subjects with AEs, SAEs, and clinically significant laboratory abnormalities.
- Assessment of changes over time in clinical laboratory parameters, vital signs, and physical examination findings.
- Incidence and titer of ADAs to OKZ, incidence of neutralizing antibodies, and the time course of antibodies.

Methodology:

The CREDO 1 study includes a 4-week Screening Period, a double-blind Treatment Period from Week 0 to Week 24, and a Safety Follow-Up Period from Week 24 to Week 44.

Subjects will be assessed for eligibility to enter the study during a 4-week Screening Period. At randomization, a total of 420 eligible subjects will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio:

1. OKZ 64 mg q4w: SC injection of OKZ 64 mg q4w (alternating with SC injection of placebo OKZ q4w to maintain blinding) + MTX.
2. OKZ 64 mg q2w: SC injection of OKZ 64 mg q2w + MTX.
3. Placebo: SC injection of placebo q2w + MTX.

Throughout the double-blind Treatment Period, all subjects will be required to remain on a stable dose of background MTX at 15 to 25 mg/week (or ≥10 mg/week if there is documented intolerance to higher doses) with a stable route of administration, and concomitant treatment with folic acid ≥5 mg per week or equivalent is required for all subjects. The last dose of study treatment (OKZ or placebo) will be at Week 22 in all groups. Following Visit 2 (randomization), subjects will return to the study site at least every other week through Week 24 for response and safety assessments as per the study Schedule of Events. Blood samples to assess

OKZ concentrations in plasma will be collected periodically throughout the Treatment Period as outlined in the study Schedule of Events.

Subjects will be classified in terms of their response to study treatment at Week 14, with nonresponders defined as subjects in any treatment group who do not improve by at least 20% in both swollen and tender joint counts (66-68 joint assessment). Starting at or as close as possible to Week 14, nonresponders will be administered sulfasalazine and/or hydroxychloroquine as rescue medication in addition to the assigned treatment.

After completion of the 24-week double-blind Treatment Period, subjects will either roll over into the long-term open-label extension (OLE) study or enter the Safety Follow-Up Period. During the Safety Follow-Up Period, subjects will return for visits +4, +8, and +22 weeks after the last dose of study treatment at Week 22 as per the Schedule of Events (Visits SFU-1 [Week 26], SFU-2 [Week 30], and SFU-3 [Week 44], respectively).

Adverse events will be assessed throughout the study period (starting when the subject signs the ICF) and evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Subjects who discontinue the randomized treatment prematurely will be required to come for the End of Treatment (EoT) Visit 2 weeks after the last study treatment administration and then continue with the scheduled study visits as per the Schedule of Events.

There will be ongoing monitoring of safety events, including laboratory findings, by the Sponsor or the Sponsor's designee. In addition, safety will be assessed throughout the study by an independent Data Safety Monitoring Board (DSMB).

Planned number of subjects:	A total of 420 subjects will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio (140 subjects per treatment group).
Treatment population:	Subjects with moderately to severely active RA and an inadequate response to treatment with MTX therapy.
Diagnosis and main criteria for inclusion:	Male or female subjects ≥18 years of age with diagnosis of moderately to severely active adult-onset RA and an inadequate response to treatment with MTX therapy.
Test product, dose and mode of administration:	Olokizumab is a humanized monoclonal antibody specific for interleukin-6 (IL-6). Subjects randomized to receive OKZ will be administered OKZ 64 mg via SC injection by blinded study site staff either q2w or q4w, depending on the randomization group.
Reference therapy, dose, and mode of administration:	Placebo: The placebo will contain no active pharmaceutical ingredients. Placebo will be administered in a blinded manner (e.g., in blinded syringes with the same appearance as syringes containing OKZ). Subjects randomized to the placebo group will be administered placebo by blinded study site staff via SC injection q2w. To maintain the blind, subjects randomized to receive OKZ q4w will also receive placebo injections at the alternate q4w interval (e.g., Week 2, Week 6, etc). Placebo will be administered in blinded syringes with the same appearance as syringes containing OKZ. MTX: Subjects in all 3 treatment groups will continue their concomitant background therapy (MTX) at a stable dose of 15 to 25 mg/week (or ≥10 mg/week if there is documented intolerance to higher doses) with a stable route of administration (oral, SC, or intramuscular [IM]).

Statistical Methods:

Calculation of Sample Size

Given that the study will be considered successful if at least 1 of the 2 OKZ dose regimens is shown to be efficacious and that a priori both OKZ dose regimens are assumed to be efficacious, disjunctive power (i.e., a probability of detecting a significant treatment effect for at least 1 OKZ treatment regimen) will be used as a criterion for the estimation of the sample size. Sample size requirements are calculated to provide sufficient disjunctive power to evaluate the primary endpoint (ACR20 response rate at Week 12) and the first secondary endpoint (DAS28 [CRP] <3.2 at Week 12). Sample size was estimated taking into account a multiplicity control procedure and the resulting α adjustment that will be used in this study to control an overall Type I error rate in the strong sense at a 1-sided $\alpha = 0.025$ across the primary and secondary endpoints. For the first secondary endpoint, the disjunctive power represents a probability of establishing a significant treatment effect for 1 or 2 OKZ dose regimens for the primary endpoint and a significant treatment effect for 1 or 2 OKZ dose regimens for the first secondary endpoint, conditional on the fact that each dose regimen tested for the secondary endpoint must have the null hypothesis previously rejected for the primary endpoint based on a fixed order of testing as per the gate-keeping procedure.

Treatment effect assumptions used in the simulation-based sample size calculations, involving the primary and the first secondary endpoints are as follows.

The ACR20 response rate at Week 12 for the placebo group is estimated to be 25% in this study population. The OKZ ACR20 response rates for the 64 mg q4w and q2w treatment groups at Week 12 are expected to be at least 50% and 55% respectively, resulting in an expected difference in ACR20 response rates of 25 and 30 percentage points between respective OKZ treatment groups and placebo.

The DAS28 low disease activity (based on DAS28 [CRP] <3.2) response rate at Week 12 is estimated to be 10% in the placebo group and 22% and 30% in OKZ 64 mg q4w and q2w treatment groups, respectively, resulting in an expected difference of 12 and 20 percentage points between respective OKZ treatment groups and placebo.

The references cited above for ACR20 and DAS28 response rates are assumed to reflect approximately 10% of subjects discontinuing randomized treatment prior to Week 12. In this study, subjects who discontinue prior to Week 12 will be classified as nonresponders for the primary endpoint of ACR20 at Week 12 as well as for the secondary endpoint of DAS28 (CRP) <3.2 at Week 12.

The primary endpoint as well as the secondary endpoints that are binary in nature will be analyzed using a 2×2 chi-squared test for equality of proportions for each OKZ treatment group compared with placebo.

Based on the treatment effect assumptions and the methodology for estimating sample size via simulation to ensure sufficient disjunctive power as described above, a sample size of 420 subjects randomized in a 1:1:1 ratio (140 subjects per treatment group) will yield 100% disjunctive power for testing the primary hypothesis (ACR20 at Week 12) and 98% disjunctive power for the evaluation of the secondary endpoint of DAS28 (CRP) <3.2 rate at Week 12.

Analysis Populations

- Intent-to-treat (ITT) population: The ITT population will include all randomized subjects. Subjects will be analyzed according to the treatment group to which they were randomized. The ITT population will be the primary analysis population.
- Modified Intent-to-treat (mITT) population: The mITT population will include all randomized subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to the treatment group to which they were randomized. The mITT population, if sufficiently different from the ITT population (>5% of ITT subjects excluded from mITT across all treatment groups), will be used for supportive analyses of the primary and secondary efficacy endpoints.
- Per Protocol (PP) population: The PP population will include all ITT subjects who do not have any major protocol violations. Subjects will be analyzed according to the treatment group to which they were randomized. Major protocol violations and the inclusion of subjects in the PP population will be finalized prior to study unblinding. The PP population will be used for supportive analyses of the primary and secondary efficacy endpoints.

- Safety population: The safety population will include all subjects who receive at least 1 dose of study treatment. Subjects in the safety population will be analyzed according to the treatment they actually received. In addition to the primary safety analysis, the incidence of AEs will be analyzed separately for subjects administered an additional disease-modifying anti-rheumatic drug (DMARD) as rescue medication during the period of treatment without rescue medication and with rescue medication.
- Pharmacokinetics population: The PK population will include all subjects who receive at least 1 dose of OKZ and have sufficient plasma samples for PK assessments without important protocol deviations or events affecting the PK results. All subjects in the PK population must have at least 1 evaluable postdose OKZ concentration. To be included in the sample-rich PK subpopulation, subjects must have received at least 1 dose of OKZ, received OKZ on Week 0, and have sufficient plasma samples to allow calculation of at least 1 PK parameter.

Efficacy Analysis

Efficacy analyses will be conducted using the ITT population. Supportive analyses of the primary and secondary efficacy endpoints will also be conducted using the mITT (if sufficiently different from the ITT population) and PP populations. All comparisons for efficacy assessments will be carried out based on treatment groups to which the subjects were originally randomized.

No adjustment for covariates will be included in the primary analysis of the primary endpoint or the analysis of the secondary and other endpoints that are binary in nature. Analyses of the continuous efficacy endpoints will be adjusted for baseline values of the corresponding parameters.

Endpoints that are binary in nature will be analyzed using a 2×2 chi-squared test for equality of proportions for each OKZ treatment group compared with placebo. Endpoints that are continuous in nature will be analyzed using an analysis of covariance (ANCOVA) model including a fixed effect for treatment and adjusted for the baseline value of the corresponding parameter.

Other statistical methods and models will be used to investigate sensitivity to missing data and adherence to randomized treatment.

Multiplicity Adjustment

Each of the OKZ treatment groups (64 mg q2w and 64 mg q4w) will be compared with placebo for each of the primary, secondary, and other endpoints. The overall Type I error rate will be controlled for testing hypotheses of the primary and secondary endpoints at the overall 1-sided $\alpha = 0.025$. The α-control strategy will be based on using the Bonferroni adjustment for the tests related to each of the 2 OKZ dose regimens versus placebo (i.e., using the 1-sided $\alpha = 0.0125$ for each dose regimen). A gate-keeping strategy will be used for tests associated with the primary and secondary endpoints for each OKZ dose regimen independently with the same order of testing as the secondary endpoints are defined above. In other words, each OKZ dose regimen will be tested at 1-sided $\alpha = 0.0125$ for a given endpoint if null hypotheses are rejected at 1-sided $\alpha = 0.0125$ for this dosing regimen for all previous endpoints based on the established order. Conversely, the testing will stop for a given OKZ dose regimen at the endpoint for which the null hypothesis is accepted at 1-sided $\alpha = 0.0125$.

Pharmacokinetic Analysis

In the subjects with periodically collected OKZ concentrations, OKZ results will be summarized descriptively by scheduled collection time and dose regimen. Time to steady state will be graphically evaluated for the OKZ trough data collected over the study period.

For the PK subpopulation, PK parameters for OKZ will be summarized descriptively by dose regimen. Accumulation over time will be evaluated descriptively, and, if appropriate, with an exploratory inferential analysis. Pharmacokinetic/PD relationships will be explored graphically and with linear or non-linear modeling approaches, as appropriate. Data collected in this study may be combined with data from other OKZ studies in support of population PK analyses. Olokizumab concentration for the ADA/PK matched subjects will only be analyzed and presented as part of the PK summaries if the subject has a positive ADA response during the Treatment Period. These data will be included the population PK analyses, as appropriate.

Safety Analysis

Major components for the safety analysis will include:

- AEs will be solicited at every study visit, recorded, and coded according to the most recent version of

the Medical Dictionary for Regulatory Activities (MedDRA).

- SAEs
- Vital signs and physical examination findings
- Laboratory parameters
- Electrocardiogram (ECG) and other specialized test findings

All AEs will be analyzed in terms of descriptive statistics and qualitative analysis. Adverse events will be listed for each subject and summarized by system organ class (SOC) and preferred term (PT) according to the most recent version of the MedDRA. In addition, summaries of AEs by severity and relationship to study treatment will be presented. All safety and tolerability data recorded during the study will be listed and summarized by treatment group, and over time, as appropriate.

Safety results will be summarized and presented with particular focus on safety concerns identified as AESIs, based either upon the safety data available to date for OKZ or drug class-related events for a biologic IL-6 inhibitor.

Cardiovascular Risk Assessment

The RA population is known to have an increased risk of CV events. To fully assess the CV risks associated with OKZ, the following approach will be used:

1. Potential major adverse cardiac events (MACE) will be adjudicated by an independent Cardiovascular Adjudication Committee (CVAC) according to a predefined charter. The charter will define the criteria, data, and source documentation required to adjudicate all MACE.
2. Baseline CV risks including individual risk factors (e.g., tobacco use, presence of hypertension, diabetes mellitus, and lipid profile) will be assessed.
3. Known CV risk factors will be monitored and assessed to detect any trends related to long-term exposure.

Safety Follow-up Assessments

Given the long half-life of OKZ (approximately 31 days), all subjects will be followed for approximately 5 OKZ half-lives (i.e., 22 weeks) after the final dose of study treatment.

Subjects who discontinue randomized treatment early (i.e., prior to Week 24) will adhere to the established double-blind Treatment Period visit schedule outlined in the study Schedule of Events, as if they were still receiving study treatment. In addition, all subjects who discontinue study treatment early will undergo a full safety assessment at the EoT Visit +2 weeks after the last dose of study treatment (OKZ or placebo), as well as extended Safety Follow-Up assessments +4, +8, and +22 weeks after the last dose of study treatment.

For subjects remaining on randomized therapy until the last scheduled dose of study treatment and not entering the OLE study, the EoT Visit will be performed at Visit 15 (Week 24) and extended Safety Follow-Up Visits will be scheduled for +4, +8, and +22 weeks after the last dose of study treatment (i.e., Visits SFU-1 [Week 26], SFU-2 [Week 30], and SFU-3 [Week 44], respectively).

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% response criteria
ACR50	American College of Rheumatology 50% response criteria
ACR70	American College of Rheumatology 70% response criteria
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCOVA	analysis of covariance
anti-CCP	anti-citrullinated protein antibody
anti-HBc	total hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ApoB	apolipoprotein B
ApoA1	apolipoprotein A1
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
$AUC_{(0\text{-}tau)}$	area under the plasma concentration-time curve over the dosing interval
bDMARD	biologic disease-modifying anti-rheumatic drug
BNP	brain natriuretic peptide
BP	blood pressure
CBC	complete blood count
CDAI	Clinical Disease Activity Index
CDC	Centers for Disease Control and Prevention
cDMARD	conventional disease-modifying anti-rheumatic drug
CDR	complementarity determining region
CL/F	apparent systemic clearance
C_{max}	maximum plasma concentration
CRP	C-reactive protein

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVAC	Cardiovascular Adjudication Committee
CYP	cytochrome P
DAS28	Disease Activity Score 28-joint Count
DMARD	disease-modifying anti-rheumatic drug
dsDNA	double-stranded DNA
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D VAS	European Quality of Life-5 Dimensions Visual Analog Scale
ESR	erythrocyte sedimentation rate
EoT	End of Treatment
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
GCP	Good Clinical Practice
GI	gastrointestinal
GGT	gamma-glutamyl transferase
gp80	interleukin-6 receptor alpha chain
gp130	interleukin-6 receptor signal-transducing subunit
HAQ-DI	Health Assessment Questionnaire - Disability Index
HbA_{1c}	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay

Abbreviation	Definition
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IM	intramuscular
INR	International Normalized Ratio
IRB	Institutional Review Board
IP	interphalangeal(s)
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous(ly)
IWRS	Interactive Web Response System
LDL	low-density lipoprotein
LFT	liver function test
LS	least squares
LTBI	latent tuberculosis infection
mAb	monoclonal antibody
MACE	major adverse cardiac event
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MCP	metacarpophalangeal
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
MTP	metatarsophalangeals
MTX	methotrexate
n	number of available values
NOAEL	no observed adverse effect level
NSAIDs	non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro-hormone of brain natriuretic peptide
OKZ	Olokizumab
OLE	open-label extension
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PEF	peak expiratory flow

Abbreviation	Definition
PG	pharmacogenetic(s)
PIP	proximal interphalangeals
PK	pharmacokinetic(s)
PP	Per Protocol
PRO	patient-reported outcome
PT	preferred term
q2w	once every 2 weeks
q4w	once every 4 weeks
QALY	quality-adjusted life years
qs	quantum satis (sufficient quantity)
R	randomization
RA	rheumatoid arthritis
R_{ac}	accumulation ratio
RBC	red blood count
RF	rheumatoid factor
SAA	serum amyloid A
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SDAI	Simplified Disease Activity Index
SF-36	Short Form-36
SJC	swollen joint count
SOC	system organ class
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
t_{max}	time to maximum plasma concentration
TNF-α	tumor necrosis factor-α
TNFi	tumor necrosis factor-α inhibitor
ULN	upper limit of normal
US	United States

Abbreviation	Definition
VAS	Visual Analog Scale
WBC	white blood count
WHO	World Health Organization
WHO DDE	World Health Organization Drug Dictionary Enhanced
WPS-RA	Work Productivity Survey – Rheumatoid Arthritis

2. INTRODUCTION

2.1 Background

Rheumatoid arthritis (RA) is a chronic immune/inflammatory disease characterized by persistent synovitis, with synovial cell proliferation and destructive changes in bone and cartilage of multiple joints. Untreated, RA can lead to destruction, deformation, and dysfunction of affected joints, which may result in significant morbidity, and accelerated mortality (Jacobsson et al, 2007). Moderately to severely active RA is often treated with disease-modifying anti-rheumatic drugs (DMARDs), with methotrexate (MTX) being the most commonly used conventional DMARD (cDMARD). For subjects with an inadequate response to cDMARDs, biologic agents (i.e., biologic DMARDs [bDMARDs]) are the next step, and include, but are not limited to, tumor necrosis factor-α (TNF-α) inhibitors (TNFi), interleukin-6 (IL-6) receptor (IL-6R) antagonists, and T-cell co-stimulation modulators. Among these, TNFi, especially in combination with MTX, are used most often (Smolen et al, 2014). Despite early treatment with cDMARD and/or bDMARD therapy, approximately 30% to 40% of subjects with established RA fail to respond and 50% to 60% of subjects fail to achieve a major clinical American College of Rheumatology (ACR) response or good European League Against Rheumatism (EULAR) response (Marchesoni et al, 2009; Rubbert-Roth and Finckh, 2009; Cohen et al, 2008). Even among responders, the majority do not achieve remission. Thus, there continues to be an unmet medical need for new therapeutic approaches in the RA patient population.

One such therapeutic approach is to target IL-6 directly instead of indirectly via a receptor antagonist. Interleukin-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts. It is involved in multiple immunologic processes such as T-cell activation, B-cell proliferation, initiation of acute-phase response, stimulation of hematopoietic precursor cell growth, differentiation and trafficking, as well as osteoclast differentiation which subsequently contributes to joint destruction. Due to the key role played by IL-6 in several RA mechanisms, targeting IL-6 is considered an attractive therapeutic option.

2.2 Study Treatment

2.2.1 Olokizumab

Olokizumab (OKZ; CDP6038; L04041) is being developed by R-Pharm for the treatment of moderately to severely active RA. Olokizumab was previously developed by UCB Pharma SA, and was transferred to R-Pharm for further global development.

Olokizumab is a humanized (complementarity determining region [CDR]-grafted) monoclonal antibody (mAb) of immunoglobulin (Ig) G4/kappa isotype, developed as an antagonist of IL-6 that is anticipated to have utility in a wide range of autoimmune/inflammatory conditions.

Interleukin-6 is a multifunctional cytokine that has been shown to play a central role in immune regulation, inflammation, hemopoiesis, and oncogenesis, and has been linked to a wide range of human diseases. It is a glycoprotein of 184 amino acids that is produced by a wide range of cell types including monocytes/macrophages, fibroblasts, epidermal keratinocytes, vascular endothelial cells, renal mesangial cells, glial cells, chondrocytes, T and B cells, and some tumor cells. Stimuli of IL-6 production include TNF-α, lipopolysaccharides, and viral infections; inhibitors of IL-6 production include glucocorticoids. Within the context of an immune and inflammatory response, IL-6 has been shown to exert a wide range of effects, such as those described below:

- Induction of antibody production by B cells
- Important role in the generation of a subpopulation of T-helper cells, Th17 cells, which may play an important pathogenic role in a number of autoimmune diseases
- Key driver of the acute phase response (the increased production, mainly by the liver, of soluble factors, such as C-reactive protein [CRP] and serum amyloid A [SAA], during inflammation)

In developing an antagonist mAb to IL-6, potential therapeutic strategies include inhibition of non-signaling IL-6R alpha chain (gp80), which gives the IL-6 family members their specificity, and the IL-6R signal-transducing subunit (gp130). The identification of the optimum epitope to target on IL-6 (binding IL-6 in a region that is predicted to be involved with gp80 or gp130) was conducted using antibodies with similar affinities, but different binding axes, as determined by surface plasmon resonance (BIAcore). Antibodies directed against mouse or human IL-6 that targeted the gp130 axis were more potent than those that targeted the gp80 axis in inhibiting IL-6-dependent phosphorylation of signal transducer and activator of transcription 3 in in vitro cell based assays and in inhibiting the secretion of the acute phase protein SAA in vivo. Olokizumab binds to a region of IL-6 involved with gp130 binding. The epitope recognized by OKZ was initially established by BIAcore and confirmed by nuclear magnetic resonance studies. Olokizumab has been shown to have a high affinity for human IL-6 as determined using BIAcore analysis. In vitro whole blood and cell line assays as well as animal studies have shown that OKZ potently neutralizes IL-6-mediated effects in vitro and in vivo, respectively. Data suggest that OKZ neither significantly binds to nor affects the function of other IL-6 family members, nor does it appear to activate the IL-6 signaling pathway under a range of conditions tested.

Currently, patients with moderately to severely active RA are often treated with cDMARDs, with MTX being the most commonly used. For patients with an inadequate response to cDMARDs, biologic agents which inhibit TNF-α, especially in combination with MTX, are indicated (Smolen et al, 2014). Nonetheless, a substantial proportion of patients receiving biologics (i.e., approximately 40% to 50% of those receiving TNFi therapy) have inadequate response to such treatment (Marchesoni et al, 2009; Rubbert-Roth and Finckh, 2009; Cohen et al, 2008). Thus, there is an unmet need for new therapeutic approaches utilizing alternative modes of action in this patient population.

Olokizumab is being developed to address the unmet needs of patients with these severe, progressive, and debilitating disorders through a different therapeutic approach, utilizing an alternative mode of action. Within the class of therapeutic antibodies targeting the IL-6 pathway, OKZ is anticipated to be more potent because of its high affinity for IL-6 and its axis of intervention (inhibiting the interaction between IL-6 and gp130). Also, since OKZ is of the Ig G4 isotype, it would not be expected to mediate significant levels of antibody-mediated complement fixation or cell-mediated cytotoxicity.

Olokizumab is being developed for the treatment of RA to reduce signs and symptoms of disease, improve physical functioning, and induce higher levels of response. The proposed indication for OKZ is to be used in combination with MTX for the treatment of moderately to severely active RA in adult patients who have been inadequately controlled by MTX treatment. A separate study is planned to address the use of OKZ in a similar RA population who are either inadequately controlled or intolerant to previous TNF-α inhibitor therapy.

Refer to the most recent version of the Investigator's Brochure for additional information on OKZ including:

- In vitro activity
- Nonclinical pharmacokinetics (PK) and product metabolism
- Nonclinical pharmacology and toxicology
- PK, efficacy, and safety profile in clinical studies

2.2.2 Nonclinical Development

Nonclinical studies have shown that inhibition of IL-6 signaling does not result in any life threatening effects either in animal models or formal toxicology studies. There is no evidence from in vitro and in vivo nonclinical data to suggest that there is a risk of OKZ inducing an uncontrolled biological cascade. All nonclinical data generated to date are consistent with OKZ functioning as an effective antagonist of the IL-6 pathway. Cellular

in vitro assay data suggest that OKZ neutralizes the biological effects of IL-6 in both humans and cynomolgus monkeys with similar potency. Therefore, the cynomolgus monkey is considered an appropriate species to evaluate the potential toxicity of OKZ. Due to the lack of activity of OKZ on IL-6 in rats and mice, the toxicology program was restricted to using a single non-rodent species, the cynomolgus monkey.

Olokizumab is well tolerated in the cynomolgus monkey, with a no observed adverse effect level (NOAEL) of 200 mg/kg/week and 50 mg/kg/week after intravenous (IV) and subcutaneous (SC) administration, respectively.

In a study aimed at assessing the effects of OKZ on prenatal and postnatal development in the cynomolgus monkey, the treatment was well tolerated during the pregnancy and had no abortifacient effect. However, some OKZ-treated females experienced dystocia and placental retention, sometimes associated with significant urogenital bleeding, which resulted in some deaths. Given similar human and cynomolgus monkey physiology during pregnancy and the risk of dystocia and hemorrhage at parturition, inhibition of IL-6 signaling during pregnancy is not recommended.

Taken together, the currently completed nonclinical studies support continued clinical development for marketing approval of OKZ.

2.2.3 Summary of Clinical Experience

Nonclinical data were deemed sufficient to support clinical development of OKZ in humans for the treatment of moderately to severely active RA (lead indication), other auto-immune inflammatory diseases, and oncological diseases with IL-6 pathophysiology.

The safety, efficacy, and PK of OKZ have been investigated in 3 Phase I clinical studies (RA0001, RA0010, and RA0074) and 2 Phase II clinical studies (RA0056 and RA0083). The safety and efficacy of OKZ were also studied in long-term open-label extension (OLE) studies for both Phase II studies (RA0057 and RA0089).

The information in this section of the protocol regarding clinical studies with OKZ is current as of 29 January 2016 (for updated information on results of clinical studies, refer to the most recent version of the Investigator's Brochure).

2.2.3.1 Summary of Studies in the Olokizumab Clinical Program

Study RA0001

Study RA0001 was a Phase I, randomized, double-blind, placebo-controlled, dose-escalating, first-in-human study that investigated the safety and tolerability, PK, and

pharmacodynamics (PD) of IV OKZ in 67 healthy Caucasian male volunteers (33 on active drug and 34 on placebo) with a 99-day follow-up.

Study RA0010

Study RA0010 was a Phase I/IIa study to characterize the PK/PD relationship between systemic OKZ exposure and CRP suppression, following single-dose IV and SC OKZ administration to subjects with RA and to evaluate the safety and tolerability of single doses of OKZ in RA subjects over a therapeutic dose range (as defined by CRP suppression).

Study RA0074

Study RA0074 was a Phase I study in healthy Japanese subjects undertaken to evaluate the PK, PD, safety, and tolerability of SC OKZ prior to undertaking clinical studies in Japanese subjects with RA.

Studies RA0056 and RA0057

Study RA0056 was a Phase II, multicenter, randomized, double-blind, placebo- and active-controlled study of OKZ in 221 subjects in the United States (US) and Europe with active RA who had previously failed TNFi therapy, administered SC at various doses and frequencies to evaluate the efficacy relative to placebo. Eligible subjects were randomized to 1 of 9 treatment groups: OKZ 60 mg SC once every 2 weeks (q2w), OKZ 60 mg SC once every 4 weeks (q4w), OKZ 120 mg SC q2w, OKZ 120 mg SC q4w, OKZ 240 mg SC q2w, OKZ 240 mg SC q4w, placebo SC q2w, placebo SC q4w, and tocilizumab 8 mg/kg IV q4w.

Study RA0057 was the long-term OLE study of RA0056, which was open for enrollment of subjects who had completed the Week 12 visit of Study RA0056. A total of 190 subjects in Study RA0057 received SC injections of OKZ 120 mg q2w throughout the study, regardless of their treatment assignment in RA0056.

Studies RA0083 and RA0089

Study RA0083 was a Phase II, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of OKZ in 119 Asian subjects with moderately to severely active RA who had previously failed TNFi therapy and were on a stable dose of MTX. Eligible subjects were randomized to 1 of 6 treatment groups: OKZ 60 mg q2w, 60 mg q4w, 120 mg q2w, 120 mg q4w, 240 mg q4w, or placebo q2w, all administered SC.

Study RA0089 was the long-term OLE study of RA0083, which was open for enrollment of subjects who had completed the Week 12 visit of Study RA0083. A total of 103 subjects in Study RA0089 received SC injections of OKZ 120 mg q2w throughout the study, regardless of their treatment assignment in Study RA0083.

2.2.3.2 Summary of Safety Data from Olokizumab Studies

Study RA0001

There were no deaths or serious adverse events (SAEs) reported during the study and no subject discontinued the study as a result of an adverse event (AE). The overall incidence of treatment-emergent adverse events (TEAEs) was slightly higher in the placebo group overall (18 subjects [52.9%]; 35 events) than in the OKZ treatment groups overall (11 subjects [33.3%]; 26 events). No increase in the incidence of TEAEs was observed with increasing dose of OKZ.

The most commonly reported TEAEs were in the system organ classes (SOCs) of gastrointestinal (GI) disorders, general disorders, and infections and infestations. The incidence of GI disorders was similar in both the OKZ group overall (12.1%) and the placebo group overall (11.8%); however, at the preferred term (PT) level, abdominal distension (1 subject [3.0%]), abdominal pain (1 subject [3.0%]), and vomiting (2 subjects [6.1%]) were only seen in the OKZ group. The most frequently reported TEAEs (occurring in ≥3% of subjects in any treatment group) by PT were influenza-like illness (11.8% placebo, 6.1% OKZ), headache (11.8% placebo, 3.0% OKZ), nasopharyngitis (8.8% placebo, 3.0% OKZ), rhinitis (8.8% placebo, 0.0% OKZ), diarrhea (5.9% placebo, 3.0% OKZ), and vomiting (0.0% placebo, 6.1% OKZ).

For the majority of hematology and clinical chemistry parameters there were no clinically significant differences in mean actual values between the placebo group and OKZ treatment groups, and no clinically significant fluctuations in mean actual values over time.

Study RA0010

There were no deaths during Study RA0010. Two subjects (1 subject in the placebo IV+MTX group and 1 subject in the OKZ 1 mg/kg SC+MTX group) experienced SAEs: Bowen's disease and worsening of RA, respectively. Neither event was considered by the Investigator to be related to the study treatment. One subject in the placebo+MTX overall group withdrew from the study as a result of exacerbation of their RA. All subjects (100%) in the placebo+MTX overall group and 96.7% of subjects in the OKZ+MTX overall group experienced at least 1 TEAE. The incidence of TEAEs did not increase with increasing dose of OKZ+MTX administered; although, a slightly higher number of AEs were experienced by subjects in the OKZ (1 mg/kg and 3 mg/kg)+MTX SC treatment groups (16 subjects [94.12%]; 101 events) compared with the OKZ (0.1 mg/kg and 1 mg/kg) + MTX IV treatment groups (13 subjects [100%]; 54 events).

Study RA0074

In Study RA0074, there were no deaths, SAEs, severe AEs, or AEs that led to discontinuation. The incidence of TEAEs was higher in the OKZ groups compared with the placebo group. In the placebo group, 50% of subjects (2 of 4) had TEAEs (6 events), compared with 75% of subjects (3 of 4) in the OKZ 3 mg/kg treatment group (11 events), and 100% of subjects (4 of 4) in each of the OKZ 0.3 mg/kg (16 events), OKZ 1 mg/kg (25 events), and OKZ 6 mg/kg (24 events) treatment groups. The incidence of TEAEs did not appear to be related to the dose of OKZ administered.

The most commonly reported TEAEs were within the SOCs of general disorders and administration site conditions; investigations; GI disorders; infections and infestations; respiratory, thoracic and mediastinal disorders; and skin and SC tissue disorders. Events occurring in >20% of subjects in the OKZ overall group, by PT, included injection site hematoma (31.3%), abdominal pain (25.0%), and alanine aminotransferase (ALT) increased (25.0%). The overall incidence of TEAEs in the OKZ-treated groups was higher than in the placebo-treated group, but given the small number of subjects in each treatment group, it is not possible to make any meaningful conclusions.

In Studies RA0001, RA0010, and RA0074, OKZ was tolerated at doses of up to 3 mg/kg SC (all studies), 6 mg/kg SC (Study RA0074 only), and 10 mg/kg IV (Study RA0001 only). There were no deaths in any of these studies and only 2 SAEs in Study RA0010. One subject in Study RA0010 discontinued the study early due to an AE (exacerbation of RA symptoms), but no subjects withdrew from Study RA0001 or Study RA0074 due to TEAEs.

Study RA0056

In Study RA0056, OKZ was well tolerated at doses of up to 240 mg q2w. Serious AEs were reported by 6 subjects in the OKZ groups and 3 subjects in the placebo groups. A total of 11 subjects in the OKZ and placebo groups discontinued due to TEAEs (10 subjects in the OKZ group and 1 subject in the placebo group). Overall, 10 subjects in the OKZ groups reported 13 TEAEs leading to discontinuation, with the most subjects discontinuing due to TEAEs in the OKZ 60 mg q4w group (5 subjects [22.7%] compared with 2 subjects [10%] in the OKZ 60 mg q2w group, 1 subject [4.5%] in the OKZ 120 mg q2w group, and 2 subjects [8.7%] in the OKZ 240 mg q2w group). One subject (4.5%) in the placebo q2w group also discontinued due to TEAEs. No TEAE PT leading to discontinuation was reported by more than 1 subject in any treatment group.

Treatment-emergent AEs were reported by 17 subjects (77.3%) in the placebo q4w group, 19 subjects (86.4%) in the placebo q2w group, 18 subjects (81.8%) in the OKZ 60 mg q4w group, 14 subjects (70.0%) in the OKZ 60 mg q2w group, 20 subjects (87.0%) in the

OKZ 120 mg q4w group, 14 subjects (63.6%) in the OKZ 120 mg q2w group, and 19 subjects each in the OKZ 240 mg q4w (86.4%) and OKZ 240 mg q2w (82.6%) groups. The majority of these TEAEs were reported during the Treatment Period.

The most commonly reported TEAEs (>10% of subjects in any treatment group) in the OKZ q4w, OKZ q2w, and placebo groups were in the SOCs of GI disorders, general disorders and administration site conditions, infections and infestations, investigations, and nervous system disorders.

The TEAEs that occurred with the greatest incidence (i.e., occurring in ≥10% of subjects) in any OKZ treatment group included: diarrhea, injection site reaction, injection site pruritus, nasopharyngitis, upper respiratory tract infection, urinary tract infection, ALT increased, aspartate aminotransferase (AST) increased, and liver function test (LFT) abnormal.

When considering TEAEs by grade according to the Common Terminology Criteria for Adverse Events (CTCAE), the majority of subjects in all treatment groups (≥59.1%) had CTCAE Grade 1 TEAEs. The CTCAE Grade 3 TEAEs included head injury, anemia, chest pain, basal cell carcinoma, injection site reaction, contusion, abscess limb, laceration, musculoskeletal pain, mania, breast discharge, breast swelling, erythema, pruritus, osteoarthritis, ligament sprain, back pain, cellulitis, and spinal cord compression. No CTCAE Grade 3 TEAE was reported by more than 1 subject. Of the CTCAE Grade 3 TEAEs, all were reported during the Treatment Period, with the exception of 1 subject in the OKZ 60 mg q4w (4.5%) group who reported CTCAE Grade 3 TEAEs during the Safety Follow-Up Period. No CTCAE Grade 4 or 5 TEAEs were observed in any treatment group. There were no deaths reported in Study RA0056. Overall, 6 subjects in the OKZ groups reported 7 SAEs (3 subjects [15.0%] reporting 3 events in the OKZ 60 mg q2w group [chest pain, basal cell carcinoma, and mania], 1 subject [4.5%] reporting 1 event in the OKZ 60 mg q4w group [LFT abnormal], and 2 subjects [9.1%] reporting 3 events in the OKZ 240 mg q4w group [pneumonia, perineal abscess, and back pain]). No subjects in the OKZ 120 mg q2w or q4w groups or in the OKZ 240 mg q2w group experienced SAEs. A total of 3 subjects in the placebo treatment groups reported 3 SAEs (2 subjects [9.1%] reporting 2 events in the placebo q2w group and 1 subject [4.5%] reporting 1 event in the placebo q4w group).

Of the SAEs reported in the OKZ groups, only LFT abnormal (1 subject [4.5%] in the OKZ 60 mg q4w group) was judged to be related to the study treatment by the Investigator. Additionally, only the SAEs of LFT abnormal (1 subject [4.5%] in the OKZ 60 mg q4w group), and chest pain (1 subject [5.0%] in the OKZ 60 mg q2w group), led to discontinuation from the study. All of the SAEs were reported as recovered/resolved with the exception of anemia (1 subject [4.5%] in the placebo q4w group).

Study RA0057

Overall, 33 subjects reported 321 TEAEs leading to discontinuation during the study. The most common TEAE PT leading to discontinuation was upper respiratory tract infection (8 subjects [4.2%]).

Three additional subjects experienced TEAEs leading to permanent discontinuation of OKZ (bladder cancer, palmar pustular dermatitis, and cholecystitis chronic). These subjects were not represented within the patient data sets or tables as this additional information was based on source documentation received from the respective study sites after the clinical database had been locked.

Treatment-emergent AEs were reported by 178 subjects (93.7%). The most commonly reported TEAEs (>10% of subjects) were in the SOCs of infections and infestations; musculoskeletal and connective tissue disorders; GI disorders; investigations; general disorders and administration site conditions; respiratory, thoracic and mediastinal disorders; skin and SC tissue disorders; injury, poisoning and procedural complications; nervous system disorders; metabolism and nutrition disorders; and vascular disorders.

When considering TEAEs by CTCAE grade, the majority of subjects had CTCAE Grade 1 (85.8%) and/or Grade 2 (56.3%) TEAEs. At the SOC level, infections and infestations was the TEAE that occurred most frequently (68.4% of subjects), with a maximum intensity of mild (102 subjects [53.7%]; 239 events), moderate (58 subjects [30.5%]; 103 events), and severe (14 subjects [7.4%]; 17 events). At the PT level, CTCAE Grade 3 TEAEs that occurred in ≥2 subjects included cellulitis, pneumonia, staphylococcal infection, urinary tract infection, back pain, RA, pulmonary embolism, and chest pain. No CTCAE Grade 3 TEAE was reported by more than 3 subjects for any PT. A total of 93 subjects (48.9%) reported TEAEs (281 events) that were judged as related to the study treatment by the Investigator. The TEAE most frequently assessed as being drug-related by the Investigator was injection site reaction SOC (21 subjects [11.1%]; 29 events).

There were 2 deaths reported in Study RA0057. The first subject experienced the treatment-emergent SAE of a road traffic accident, reported as severe and considered not related to the study treatment. The second subject had multiple co-morbidities and experienced necrotizing fasciitis, acute renal failure, multi-system organ failure, and sepsis after approximately 9 months of exposure to OKZ. Two months prior to death, OKZ was discontinued as the subject was lost to follow-up. The Investigator and Sponsor judged that necrotizing fasciitis and sepsis were related to the study treatment, and that acute renal failure and multi-system organ failure were not related to the study treatment.

A total of 50 subjects (26.3%) reported 83 treatment-emergent SAEs. The highest incidence of events was observed for the SOC of infections and infestations (19 subjects [10.0%]; 24 events). At the PT level, chest pain occurred with the highest frequency (4 subjects [2.1%]; 4 events).

Of the SAEs reported, diverticulitis (2 subjects), diverticular perforation, pneumonia, bladder cancer, furuncle, necrotizing fasciitis, sepsis, B-cell lymphoma, elevated lactate dehydrogenase, elevated liver enzymes, and cellulitis (1 subject each) were judged to be related to the study treatment by both the Investigator and Sponsor.

One SAE (maculopapular rash) was judged related to the study treatment by the Investigator, but not related by the Sponsor. One SAE (staphylococcal infection) was judged not related to the study treatment by the Investigator, but related by the Sponsor.

The remaining SAEs were judged not related to the study treatment by both the Investigator and Sponsor.

Study RA0083

Safety findings in Study RA0083 were consistent with the safety profile expected with this class of drug. Serious AEs were reported by 2 subjects (6.9%) in the placebo group and 2 subjects each in the OKZ treatment groups. Overall, 2 subjects in the placebo group, and 5 subjects in the OKZ treatment groups reported a total of 9 TEAEs leading to discontinuation. Discontinuations due to TEAEs were reported by very few subjects in any 4-week cumulative dose group: 2 subjects each in the placebo, OKZ 60 mg, and OKZ 240 mg groups and 1 subject in the OKZ 120 mg group. Of the 7 subjects overall who discontinued due to TEAEs, a similar number of subjects discontinued during the Treatment Period (3 subjects overall) and the Safety Follow-Up Period (4 subjects overall). With the exception of 2 subjects in the placebo group who discontinued due to RA exacerbation, no TEAE PT leading to discontinuation was reported by more than 1 subject in any treatment group.

Treatment-emergent AEs were reported at similar incidences across the OKZ 4-week cumulative dose groups and the placebo group.

The most commonly reported TEAEs (>10% in any treatment group) were in the SOCs of infections and infestations, GI disorders, general disorders and administration site conditions, hepatobiliary disorders, nervous system disorders, and skin and SC disorders. Nasopharyngitis, headache, and rash occurred with the greatest incidence in the all OKZ group. The incidence of diarrhea was higher in the placebo group than the all OKZ group.

The incidence of TEAEs of hepatic function abnormal and nasopharyngitis increased with higher cumulative doses of OKZ.

When considering TEAEs by CTCAE grade, there were no Grade 4 or 5 TEAEs.

The majority of subjects across all 4-week cumulative dose groups (≥56.3%) had CTCAE Grade 1 TEAEs. Three subjects reported Grade 3 TEAEs: 1 subject in the OKZ 120 mg 4-week cumulative dose group reported face edema and 2 subjects in the placebo group reported exacerbation of RA.

Treatment-emergent AEs considered related to the study treatment by the Investigator were reported at a higher incidence across the OKZ 4-week cumulative dose groups compared with the placebo group. The overall incidence of drug-related TEAEs was highest in the OKZ 60 mg 4-week cumulative dose group. The most commonly reported individual drug-related TEAEs were nasopharyngitis, stomatitis, injection site erythema, rash, and headache. The incidences of drug-related TEAEs of injection site erythema, injection site swelling, and nasopharyngitis were highest in the OKZ 240 mg 4-week cumulative dose group. There were no deaths reported in any treatment group during Study RA0083. Serious TEAEs were reported by 2 subjects (6.9%) in the placebo group (RA in both subjects; both events led to study discontinuation and were considered resolved after 44 days) and 1 subject each (3.1% and 3.8%) in the OKZ 60 and 240 mg 4-week cumulative dose groups (cellulitis and pneumonia, respectively). No SAEs were reported by subjects in the OKZ 120 mg 4-week cumulative dose group. Both the cellulitis and pneumonia SAEs in subjects receiving OKZ were reported as moderate in intensity and not related to the study treatment. The cellulitis event led to study discontinuation and resolved after 11 days. The pneumonia event required hospitalization, but the subject continued in the study and the event resolved after 57 days.

Study RA0089

Overall, 7 subjects (6.8%) reported 33 TEAEs leading to discontinuation during the study. The mostly commonly reported TEAEs leading to discontinuation were in the SOC of infections and infestations (5 subjects [4.9%]).

Treatment-emergent AEs were reported by 90 subjects (87.4%). The most commonly reported TEAEs (>10% of subjects) were in the SOCs of infections and infestations; GI disorders; general disorders and administration site condition; skin and subcutaneous tissue disorders; investigations; injury, poisoning and procedural complications; respiratory, thoracic and mediastinal disorders; musculoskeletal and connective tissue disorders; nervous system disorders; eye disorders; metabolism and nutrition disorders; and vascular disorders.

When considering TEAEs by CTCAE grade, the majority of subjects (89 subjects [86.4%]; 571 events) had CTCAE Grade 1 TEAEs. At the SOC level, infections and infestations occurred most frequently (65.0% of subjects) with a maximum intensity of mild (62 subjects [60.2%]; 135 events), moderate (9 subjects [8.7%]; 16 events), or severe (4 subjects [3.9%]; 4 events).

A total of 73 subjects (70.9%) reported TEAEs that were judged to be related to the study treatment by the Investigator. Within the SOC of infections and infestations, 44 subjects (42.7%) reported 89 TEAEs that were judged to be related to the study treatment by the Investigator.

There were no deaths reported in Study RA0089.

A total of 14 subjects (13.6%) reported 20 SAEs. The highest incidence of events was observed for the infections and infestations SOC (7 subjects [6.8%]). At the PT level, cellulitis occurred with the highest frequency (2 subjects [1.9%]; 2 events). No other PT was reported more than once.

Of the SAEs reported, cellulitis (2 subjects), gastroenteritis, pleurisy, pneumonia, elevated liver enzymes, pulmonary tuberculosis (TB), interstitial lung disease, and epiglottitis (1 subject each) were judged to be related to the study treatment by both the Investigator and Sponsor.

One SAE (infectious pleural effusion) was judged to be related to the study treatment by the Investigator, but not related by the Sponsor.

There was 1 subject who reported an SAE of pulmonary TB that was considered by the Investigator to be related to OKZ. The subject had no history of active or latent TB, chronic productive cough, persistent fever, persistent asthenia, human immunodeficiency virus (HIV) infection, or organ transplants. Chest imaging revealed increased infiltration of bilateral lung fields, borderline heart size, and calcified lesion over the left aspect of the upper mediastinum. Chest X-ray and bronchial culture were positive for TB, and the diagnosis was confirmed by acid fast bacillus stain. The subject was treated with 250 mg tranexamic acid 4 times per day/capsule, rifampin 5 tablets daily, and ethambutol 800 mg daily for TB. There was no action taken with OKZ due to the event, as the event was confirmed during the follow-up period of the study, after the last dose of study treatment had been administered. The subject completed the entire anti-TB treatment course, and the event resolved. The Investigator and the Sponsor assessed the event to be related to OKZ.

2.2.3.3 Summary of Efficacy Data from Olokizumab Studies

Study RA0010

Preliminary efficacy data in terms of the Disease Activity Score 28-joint Count (DAS28) (CRP) were obtained in Study RA0010. An indication of the efficacy of OKZ was obtained in the subpopulation of subjects with a baseline DAS28 (CRP) of >3.2 (i.e., those with moderate to high disease activity). Although the number of subjects falling into this moderate to high category was small, improvements in DAS28 (CRP) were seen following OKZ+MTX administration, especially in the OKZ 1 mg/kg SC+MTX group.

Study RA0056

In Study RA0056, a greater improvement in least squares (LS) mean DAS28 (CRP) from baseline at Week 12 was observed across all OKZ treatment groups compared with the placebo groups, with the greatest improvement observed in the OKZ 240 mg q2w group. The overall dose-response trend (across the q4w and q2w dosing frequencies) was statistically significant ($p<0.0001$). Comparisons of dosing frequency (q2w versus q4w) and dose-by-dose frequency interactions (q2w trend versus q4w trend) were not statistically significant. The secondary efficacy variables were ACR 20% (ACR20), 50% (ACR50), and 70% (ACR70) response criteria at Week 12 for the OKZ and placebo treatment groups. The ACR20 and ACR50 estimated response rates at Week 12 were higher in all OKZ treatment groups compared with the placebo groups. Very few subjects in any treatment group were ACR70 responders; however, those subjects who were ACR70 responders were all in the OKZ treatment groups.

Study RA0083

In Study RA0083, a greater improvement in LS mean change from baseline in DAS28 (CRP) at Week 12 was observed across all OKZ 4-week cumulative dose groups compared with the placebo group, with the greatest improvement observed in the OKZ 240 mg 4-week cumulative dose group. The overall dose-response trend (for the 4-week cumulative dose) was statistically significant ($p<0.0001$), as were the differences between each treatment group versus placebo ($p<0.0001$ for each treatment group). The comparisons of dosing frequency (OKZ 120 mg group [60 mg q2w versus 120 mg q4w] and OKZ 240 mg [120 mg q2w versus 240 mg q4w]), dosing frequency effect (q4w versus q2w dose frequency), and dose frequency interactions (individual doses by dose frequency interaction) were not statistically significant. The ACR20 and ACR50 estimated response rates at Week 12 were higher in all OKZ 4-week cumulative dose groups compared with the placebo group. The overall dose-response trend at Week 12 was statistically significant, as were all treatment

group comparisons versus placebo. Very few subjects were ACR70 responders; however, 14 of the 15 subjects who were ACR70 responders were in OKZ treatment groups.

Study RA0057

Study RA0057 was designed to collect safety data and had no primary efficacy endpoints; however, some trends could be identified. All treatment groups described in Study RA0057 belong to Study RA0056, from which the subjects were transferred to a single treatment group of 120 mg q2w in Study RA0057. The change in DAS28 (CRP) was summarized at Weeks 12, 24, and 48 relative to baseline (Week 0) in Study RA0056 and baseline in Study RA0057. Relative to the Study RA0057 baseline, all treatment groups (except OKZ 60 mg q4w group at Week 12) showed a further decrease in DAS28 (CRP) at Weeks 12, 24, and 48. Subjects switching from the placebo group in Study RA0056 to treatment with OKZ 120 mg q2w in Study RA0057 showed a marked improvement in DAS28 (CRP), similar to the improvement shown by subjects in the OKZ groups in the parent RA0056 study. The ACR20, ACR50, and ACR70 response criteria were summarized at Weeks 0, 12, 24, and 48. Relative to the Study RA0056 baseline, a clinically relevant proportion of subjects achieved ACR20 at Week 24 across all the treatment groups, ranging from 30.0% of subjects in the OKZ 240 mg q4w group to 66.7% of subjects in the OKZ 240 mg q2w group. Fewer subjects achieved ACR50 at Week 24, ranging from 11.8% to 43.8% of subjects. Very few subjects achieved ACR70 at Week 24, ranging from 0% to 25% of subjects.

Study RA0089

All treatment groups described in Study RA0089 belong to Study RA0083, from which the subjects were transferred to a single treatment group of 120 mg q2w in Study RA0089. The baseline values in Study RA0089 corresponded to the baseline values from Study RA0083, and the Week 0 values in Study RA0089 corresponded to the Week 12 values from Study RA0083. The change in DAS28 (CRP) was summarized at Weeks 12, 24, and 48 relative to baseline (Week 0) in Study RA0083 and baseline in Study RA0089. Relative to the Study RA0089 baseline, all treatment groups showed a notable decrease in DAS28 (CRP) at Weeks 12, 24, and 48. Subjects assigned to placebo in Study RA0083 showed marked improvements in all parameters of disease activity after they began therapy with OKZ in Study RA0089, with an improvement in DAS28 (CRP) similar to the improvement shown by subjects in the OKZ groups in the parent RA0083 study. The ACR20, ACR50, and ACR70 response criteria were summarized at Weeks 0, 12, 24, and 48. Relative to the Study RA0083 baseline, a clinically relevant proportion of subjects achieved ACR20 at Week 24 across all the treatment groups, ranging from 46.7% of subjects in the OKZ 120 mg q4w treatment group to 81.8% in OKZ 240 mg q4w treatment group. Fewer

subjects achieved ACR50 at Week 24, ranging from 40.0% to 63.6% of subjects. Only a small proportion of subjects achieved ACR70 at Week 24, ranging from 10.0% to 54.5% of subjects.

2.2.3.4 Summary of Pharmacokinetic Data from Olokizumab Studies

Studies RA0001, RA0010, and RA0056

Single dose PK of OKZ were studied in Studies RA0001 (healthy non-Asian), RA0074 (healthy Japanese), and RA0010 (subjects with RA). Sparse sampling following repeated administration of OKZ was performed in non-Asian and Asian subjects with RA in Studies RA0056 and RA0083, respectively. Exposure to OKZ following single dose administration appeared to be similar in non-Asian and Asian volunteers. Following SC administration, maximum plasma concentrations (C_{max}) were generally reached between approximately 4 days (in Study RA0074, 6 mg/kg SC) and 14 days (in Study RA0001, 1 mg/kg SC). Over the 0.3 to 6 mg/kg SC dose range evaluated in Studies RA0001 and RA0074, the median terminal half-life ranged from 30.1 to 39.6 days. The PK profile of OKZ in Study RA0010 (non-Asian RA volunteers) was similar to that seen in healthy volunteers in Study RA0001 for the same doses. The maximum concentration of OKZ following SC administration was achieved within a median of 7 to 13 days following 3 mg/kg and 1 mg/kg dosing, respectively. The estimate of terminal half-life across doses and routes of administration was 31 days (median range: 12 to 63 days).

Pharmacokinetic bioavailability of OKZ via SC administration was estimated to be 63% across the 3 studies evaluated (Studies RA0001, RA0010, and RA0056). Population PK analysis utilizing sparse plasma concentration versus time data collected in RA0056 along with intense PK data collected in Studies RA0001 and RA0010 indicated similar PK characteristics of OKZ in subjects with moderately to severely active RA and in healthy subjects. Body weight was found to be the only "statistically significant" covariate on volume of distribution.

2.2.4 Rationale for Dose Selection

The dose regimens of OKZ to be evaluated in this Phase III study are 64 mg q2w and 64 mg q4w. The rationale for selecting these dose regimens for further investigation is provided below.

In the Phase II studies RA0056 and RA0083, the primary efficacy variable was met in all OKZ treatment groups, demonstrating improvement compared with placebo groups and a statistically significant overall dose-response trend as evidenced by the change from baseline in DAS28 (CRP). Study RA0001 demonstrated that OKZ was pharmacologically active at all doses tested. This finding was supported by the PD and clinical findings of the

subsequent Phase I/IIa study RA0010, conducted in subjects with mild to moderate RA. The data from these studies highlight the potency of OKZ as well as the existence of dose-response dependence, shown by the results of the concentration effect relationship evaluation for efficacy outcomes. The relatively flat concentration-effect relationship for safety outcomes and the dose-dependent occurrence of injection site reactions for the OKZ 240 mg dose regimen, in contrast to the modest efficacy gains versus the 120 mg dose regimens, led to the exclusion of the 240 mg dose regimen from further evaluation in the Phase III program. This decision was further supported by the inconvenience of administering 2 injections of 120 mg OKZ in order to achieve the 240 mg dose level even with the new 160 mg/mL formulation.

In a thorough dose-response analysis using the combined database from the 2 Phase II studies, it was confirmed that a plateau of efficacy was reached at a cumulative monthly dose of 120 mg. The 60 mg monthly dose seemed to have slightly lower efficacy in the modeling analysis, however, in both Phase II studies that were conducted in relatively difficult to treat population of subjects resistant to one or more TNFi biologics, the 60 mg monthly dose groups showed statistically significant efficacy. While there was not a detectable increase in safety events observed with doses above 120 mg monthly, there also did not seem to be a substantial gain in efficacy with higher doses. Thus, the 120 mg monthly dose, administered as either 60 mg q2w or 120 mg q4w, seemed to be associated with optimal efficacy/safety ratio. The lower 60 mg monthly dose was also efficacious with a potential for a safety advantage, especially over the long-term treatment.

Due to an increase in the concentration of the formulation subsequent to Phase II, it should be noted that the lowest volume which can be used in Phase III (0.4 mL) results in a nominal dose of 64 mg rather than 60 mg.

Consequently, using the primary efficacy outcomes from individual Phase II studies, and additional dose-response analysis performed on a combined database derived from these studies, 2 OKZ dose regimens were selected for further investigation: 64 mg SC q2w and 64 mg SC q4w since totality of the data strongly suggested that both of these dose regimens could potentially be successful in a large Phase III program.

2.3 Rationale for the Study

The double-blind, randomized, parallel-group, placebo-controlled design used in this study is consistent with the precedent set for phase III trials of other biologics and is in accordance with health authority guidelines.

The goal of this Phase III study is to assess the safety, tolerability, and efficacy of OKZ in subjects with moderately to severely active RA who have responded inadequately to MTX.

The primary endpoint of the trial is at Week 12. Olokizumab is expected to reduce the disease activity and induce an improvement in physical function. The study is expected to provide safety information in a large group of subjects over at least a 24-week period.

Due to the nature of RA and the outcome measures used (ACR response and DAS), a placebo group is necessary to obtain a reliable assessment of efficacy. The inclusion of a placebo group and the duration of placebo treatment are in accordance with health authority guidelines. Due to the availability of multiple treatment options for RA, all subjects identified as nonresponders at Week 14, including those receiving placebo, will receive rescue medication starting at or as close as possible to Week 14 (see Section 6.13.3). The inclusion of a control group with non-active treatment (placebo) is also justified because subjects will continue to receive their prior background therapy (MTX) during the study. Up to 30% of placebo subjects may still continue to demonstrate increasing therapeutic benefit over 6 months of MTX therapy at the same dose (Keystone et al, 2004).

2.4 Benefit/Risk Assessment

Olokizumab has undergone extensive nonclinical testing, and 7 clinical studies have been completed. In the difficult-to-treat population of RA patients who previously failed TNFi therapy, OKZ has demonstrated efficacy in 2 Phase II studies (Study RA0056 [extended with Study RA0057] in 221 subjects and Study RA0083 [extended with Study RA0089] in 119 Asian subjects) using the doses of OKZ that are proposed for this Phase III study; at higher doses, the safety profile was similar. Bioavailability of OKZ via SC administration was estimated to be 63% across 3 studies evaluated (RA0056, RA0001, and RA0010).

The clinical program to date suggests that OKZ is effective in reducing disease symptoms in subjects with RA, and that OKZ is generally well tolerated (for further efficacy and safety information, refer to the most recent version of the Investigator's Brochure). The safety profile of OKZ is consistent with the known effects of IL-6 blockers. Overall, the benefit/risk profile for subjects in the proposed study is favorable. The study will provide valuable information on the efficacy, safety, tolerability, and PK of OKZ in subjects with RA, which may subsequently help to address the unmet medical needs for this patient population.

The design of this study contains adequate measures to mitigate risk factors and adequate safety monitoring to protect the subjects. Nonresponders at Week 14, defined as all subjects who do not improve by at least 20% in both swollen joint counts (SJC) and tender joint counts (TJC) (66-68 joint assessment), will receive rescue medication (sulfasalazine and/or hydroxychloroquine) in addition to assigned treatment starting at or as close as possible to Week 14. In the context of the progressive, severe, and debilitating nature of RA, the

balance between risks that have been identified from cumulative safety data for OKZ and anticipated efficacy/benefits remains favorable.

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of OKZ 64 mg administered SC q2w or q4w relative to placebo in subjects with moderately to severely active RA inadequately controlled by MTX therapy.

3.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the efficacy of OKZ over time
- To compare the physical function and quality of life of subjects receiving OKZ relative to placebo
- To characterize population PK of OKZ and individual drug exposures
- To assess the safety and tolerability of OKZ

4. SUMMARY OF STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the ACR20 response at Week 12, where a responder is defined as any subject satisfying ACR20 criteria and remaining on randomized treatment and in the study at Week 12. This endpoint will serve to demonstrate that the efficacy of OKZ is superior to placebo.

4.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

- 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 24
- Percentage of subjects with Clinical Disease Activity Index (CDAI) ≤2.8 (remission) and remaining on randomized treatment and in the study at Week 24

4.3 Other Efficacy Endpoints

The following additional efficacy endpoints will be used to compare OKZ with placebo:

- Proportion of subjects achieving an ACR20, ACR50, and ACR70 response and remaining on randomized treatment and in the study, assessed at all other 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 low disease activity (based on DAS28 [CRP] <3.2) and remaining on randomized treatment and in the study, assessed at all other applicable time points

- Proportion of subjects with improvement from baseline in HAQ-DI score ≥0.22 and remaining on randomized treatment and in the study, assessed at all applicable time points
- Change from baseline over time in DAS28 (CRP)
- Change from baseline to Weeks 12 and 24 in DAS28 erythrocyte sedimentation rate (ESR)
- Change from baseline to all other applicable time points in the measure of physical ability (HAQ-DI)
- Change from baseline to Weeks 12 and 24 in the scores for the following patient-reported outcome (PRO) measures:
  - Short Form-36 (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) total scores
  - European Quality of Life-5 Dimensions (EQ-5D)
  - Work Productivity Survey-Rheumatoid Arthritis (WPS-RA)
  - Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)
- Change from baseline to all applicable time points in SDAI and CDAI
- Proportion of subjects with moderate to good responses for EULAR based on DAS28 (CRP) and remaining on randomized treatment and in the study, assessed at all applicable time points, where a moderate response is defined as either DAS28 (CRP) ≤5.1 with an improvement from baseline in DAS28 (CRP) >0.6 and ≤1.2, or DAS28 (CRP) >3.2 with an improvement from baseline in DAS28 (CRP) >1.2, and a good response is defined as DAS28 (CRP) ≤3.2 with an improvement from baseline in DAS28 (CRP) >1.2
- Change from baseline to all time points in the components of the ACR response criteria

4.4 Pharmacokinetic Endpoints

Olokizumab in plasma will be assessed as follows:

- All subjects: Blood samples for measurement of OKZ concentrations will be collected at each time a blood sample is taken for the determination of antidrug antibodies (ADAs) (ADA/PK matched subjects), with the exception of the final Safety Follow-Up Visit.

However, OKZ concentrations will only be analyzed for subjects who have a confirmed positive ADA response in any of the postdose samples

- PK Subpopulation: In approximately one third (33%) of consenting subjects, OKZ concentrations will be determined periodically throughout the study at scheduled visits
- Sample-Rich PK Subpopulation: at least 42 subjects in the PK subpopulation will be consented with an additional informed consent form (ICF) and serial blood samples will be collected following the first dose of study treatment (Week 0) and over a 4-week period at steady state (Weeks 20 through 24) to reach appropriate number of the enrolled subjects for further analysis of PK parameters. Olokizumab PK parameters will be determined in subjects randomized to OKZ following single (Week 0) and multiple dose (Week 20) administration, as appropriate. The Interactive Web Response System (IWRS) will be constructed to select consenting subjects to be included in the PK subpopulation in a blinded fashion based on the treatment group to which they are randomized. The PK parameters assessed will include, but not be limited to, C_{max}, time to maximum plasma concentration (t_{max}), area under the plasma concentration-time curve over the dosing interval ($AUC[_{0\text{-}tau}]$), apparent systemic clearance (CL/F), and accumulation ratios (R_{ac}) for C_{max} and $AUC(_{0\text{-}tau})$.

4.5 Pharmacokinetic/Pharmacodynamic Correlations

The PK and immunogenicity of OKZ will be assessed by:

- Characterizing the dose/exposure-response relationships related to efficacy endpoints (e.g., ACR20 response) and identifying potential factors that may impact the efficacy endpoints
- Characterizing the dose/exposure-response relationships related to safety endpoints (e.g., lipids and neutrophils) and identifying potential factors that may impact the safety endpoints
- Evaluating the impact of ADAs on subject safety, efficacy, and PK of OKZ

4.6 Exploratory Endpoints

- Exploratory pharmacogenetic (PG) assessments (in subjects who sign the separate PG ICF only) to examine whether individual genetic variation in genes relating to drug metabolism, RA, and the drug target pathway confers a differential response to OKZ
- Exploratory biomarker assessments aiming to identify potential markers that are associated with treatment response to OKZ, correlated with the severity or progression of RA, or are cardiovascular (CV) surrogate biomarkers

4.7 Safety Endpoints

The safety of OKZ will be assessed by:

- The nature, incidence, severity, and outcome of AEs, including SAEs and adverse events of special interest (AESIs)
- Proportions of subjects with AEs, SAEs, and clinically significant laboratory abnormalities
- Assessment of changes over time in clinical laboratory parameters, vital signs, and physical examination findings
- Incidence and titer of ADAs to OKZ, incidence of neutralizing antibodies, and the time course of antibodies

5. INVESTIGATIONAL PLAN

5.1 Summary of Study Design

This is a randomized, double-blind, parallel-group, placebo-controlled, multicenter Phase III study that will evaluate the efficacy and safety of OKZ in subjects with moderately to severely active RA inadequately controlled by MTX therapy.

Inadequate response to MTX therapy is defined as a subject with at least 12 weeks of exposure prior to Screening and with either:

- Absence of any documented clinically significant response; or
- Documented initial clinical response with subsequent loss of that response or partial response

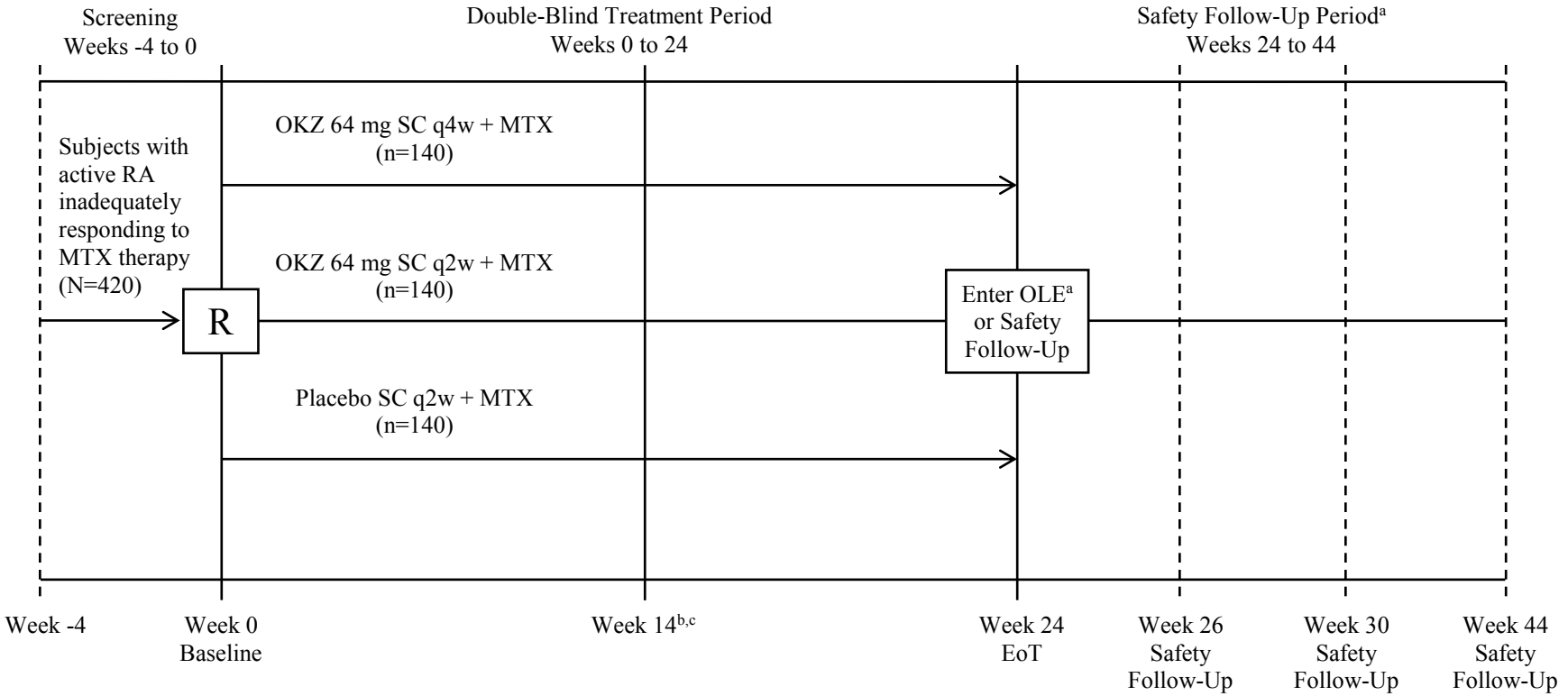
This study will be conducted at approximately 50 sites across 4 countries globally, which may include Russia, Belarus, Turkey, and Bulgaria. A total of 420 subjects will be randomized.

Subjects will be assessed for eligibility to enter the study during a 4-week Screening Period. Eligible subjects will be randomized at Visit 2 in a 1:1:1 ratio to 1 of 2 dosing frequencies (q2w or q4w) of 64 mg OKZ or to placebo as described in Section 5.2. The study will consist of a 24-week double-blind Treatment Period with the last dose of study treatment (OKZ or placebo) administered at Week 22 in all groups. After completion of the double-blind Treatment Period, subjects will be offered the opportunity to enter the long-term OLE study. Subjects who do not consent to participate in the OLE study will come to the End of Treatment (EoT) Visit (Visit 15, Week 24) 2 weeks after the last dose of the study treatment for scheduled assessments. After the EoT Visit, these subjects will be scheduled for Safety Follow-Up Visit SFU-1 (Week 26), Visit SFU-2 (Week 30), and Visit SFU-3 (Week 44) to perform adequate safety assessments. For subjects not entering the OLE, the total amount of time to complete the study will be approximately 48 weeks (inclusive of the Screening, Treatment, and Safety Follow-Up Periods).

Subjects who discontinue randomized study treatment early will adhere to the double-blind Treatment Period visit schedule outlined in Table 1 or Table 2 (as applicable), as if they were still receiving study treatment. In addition, all subjects who discontinue study treatment early will be required to attend the EoT Visit +2 weeks after the last dose of the study treatment, as well as Safety Follow-Up assessments +4, +8, and +22 weeks after the last dose of study treatment.

A schematic of the study design is presented in Figure 1. The Schedule of Events to be conducted during the initial 24-week double-blind Treatment Period (Screening through Week 24) and the Safety Follow-Up Period (Week 24 through Week 44) is presented in Table 1 for all subjects who are not part of the sample-rich PK subpopulation. For subjects who have consented in a separate, optional ICF to be included in the sample-rich PK subpopulation, the Schedule of Events is presented in Table 2.

Figure 1 CL04041022 (CREDO 1) Study Schematic



Abbreviations: DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; N = total number of subjects; n = number of subjects per treatment group; OKZ = olokizumab; OLE = open-label extension; q2w = once every 2 weeks; q4w = once every 4 weeks; R = randomization; RA = rheumatoid arthritis; SC = subcutaneous.

a. After completion of the 24-week double-blind Treatment Period, subjects will either roll over into the long-term OLE study or return for Safety Follow-Up Visits at Weeks 26, 30, and 44 in the current study.
b. At Week 14, subjects are classified as nonresponders if they do not improve by at least 20% in both swollen and tender joint counts (66-68 joint assessment).
c. Starting at or as close as possible to Week 14, subjects classified as nonresponders are prescribed 1 or both of the 2 allowed DMARDs in addition to the study treatment, background MTX, and concomitant folic acid or equivalent.

Table 1 CL04041022 (CREDO 1) Schedule of Events (Double-Blind Treatment Period and Safety Follow-Up Period)

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Window (days) for all subjects other than those included in the sample-rich PK subpopulation																		
	-28 to -1	**±0**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**
Obtain informed consent, optional PK informed consent, optional PG informed consent	✓[c]																	
Subject number assigned via IWRS	✓																	
Determine eligibility	✓	✓																
Demography	✓																	
Medical history and current medical conditions	✓																	
Height	✓																	
Weight	✓	✓			✓		✓		✓			✓			✓	✓	✓	✓
Physical examination	✓[d]	✓[d]	✓	✓	✓	✓	✓	✓	✓[d]	✓	✓	✓	✓	✓	✓[d]	✓	✓	✓[d]
Vital signs[e]	✓	✓[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraceptive history/status	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant and prior medications/non-drug therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization		✓																
Study treatment allocation through IWRS		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Administer study treatment[g]		✓[h]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Window (days) for all subjects other than those included in the sample-rich PK subpopulation																		
	-28 to -1	**±0**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**
Prescribe rescue medication for nonresponders[i]										✓								
EFFICACY ASSESSMENTS																		
Patient Global Assessment of Disease Activity (VAS)		✓		✓	✓		✓		✓			✓			✓			
Patient Assessment of Pain (VAS)		✓		✓	✓		✓		✓			✓			✓			
HAQ-DI		✓		✓	✓		✓		✓			✓			✓			
SF-36, EQ-5D, FACIT-Fatigue, and WPS-RA		✓							✓						✓			
Joint counts (Independent Joint Assessment)[j]	✓	✓		✓	✓		✓		✓	✓		✓			✓			
Physician Global Assessment VAS		✓		✓	✓		✓		✓			✓			✓			
CRP	✓[k]	✓		✓	✓		✓		✓			✓			✓	✓	✓	
ESR		✓							✓						✓			
LABORATORY/SAFETY ASSESSMENTS																		
AEs/SAEs[l]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IGRA	✓													✓				
HIV serology	✓																	
HBsAg, anti-HBs, anti-HBc, HCV Ab	✓																	
Pregnancy test[m]	✓	✓			✓		✓		✓		✓		✓		✓	✓	✓	✓

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Window (days) for all subjects other than those included in the sample-rich PK subpopulation																		
	-28 to -1	**±0**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**
INR, aPTT, fibrinogen[n]		✓			✓				✓						✓			✓
Lipid panel (fasting)[o]		✓			✓				✓						✓			✓
CV risk panel[p]		✓			✓				✓						✓			✓
HbA_{1c}	✓																	
Hematology[q]	✓[r]	✓	✓		✓		✓		✓		✓		✓		✓		✓	✓
Chemistry panel[s]	✓[r]	✓	✓		✓		✓		✓		✓		✓		✓		✓	✓
RF and anti-CCP	✓														✓			
Urinalysis[t]	✓	✓							✓						✓			✓
ANA and anti dsDNA antibody		✓													✓			✓
PG		✓[u]																
Serum biomarkers related to targeted pathway		✓			✓				✓						✓			
Assess injection site reactions[v]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
TB risk questionnaires	✓						✓			✓					✓		✓	
Chest X-ray	✓[w]														✓[x]			
12-lead ECG	✓	✓													✓			✓
PHARMACOKINETIC/IMMUNOGENICITY ASSESSMENTS																		
PK blood samples																		
All subjects		✓			✓		✓		✓				✓		✓		✓	
PK subpopulation[y]		✓	✓	✓	✓		✓		✓	✓	✓		✓	✓	✓		✓	
ADAs[z]		✓[aa]			✓		✓		✓				✓		✓		✓	✓

Abbreviations: ADA = antidrug antibody; AEs = adverse events; ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-CCP = anti-citrullinated protein antibody; anti-HBs = hepatitis B surface antibody; anti-HBc = total hepatitis B core antibody; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BP = blood pressure; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; CV = cardiovascular; dsDNA = double-stranded DNA; ECG = electrocardiogram; EoT = End of Treatment; EQ-5D = European Quality of Life – 5 Dimensions; ESR = erythrocyte sedimentation rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; GGT = gamma-glutamyl transferase; HAQ-DI = Health Assessment Questionnaire-Disability Index; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCV Ab = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; ICF = informed consent form; IEC = Independent Ethics Committee; IGRA = interferon-gamma release assay; INR = International Normalized Ratio; IRB = Institutional Review Board; IWRS = Interactive Web Response System; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide; PG = pharmacogenetic(s); PK = pharmacokinetic(s); PRO = patient-reported outcomes; RBC = red blood count; RF = rheumatoid factor; SAE = serious adverse event; SC = subcutaneous(ly); SDAI = Simplified Disease Activity Index; SF-36 = Short Form-36; TB = tuberculosis; WBC = white blood count; WPS-RA = Work Productivity Survey – Rheumatoid Arthritis; VAS = Visual Analog Scale.

Note: Data for the CDAI and SDAI endpoints will be derived from the relevant applicable efficacy assessments performed as per the above Schedule of Events.

a. As much as possible, the assessments to be performed at each study visit will be conducted in the standard order outlined in Section 5.4. At all post-randomization visits, the PRO questionnaires should be performed first, prior to any discussion between the subject and site staff.
b. The number of weeks (+2, +4, +8, or +22) after the last dose of the study treatment.
c. A separate ICF will be completed for the main study, PK subpopulation (optional), and PG (optional). Written informed consent must be obtained prior to performance of any protocol-specific procedures, including the discontinuation of any prohibited medications.
d. Complete physical examination (see Section 7.6.7.1).
e. Vital signs include temperature, heart rate, BP, and respiratory rate.
f. Blood pressure and pulse also need to be reassessed 1 and 2 hours postdose at Visit 2.
g. If desired, SC injections may be rotated among the thighs and abdomen.
h. Subjects will remain at the study site for at least 2 hours after the injection at Visit 2 to be assessed for onset of any systemic injection reactions (See Section 7.6.3.2 and Appendix 6 [Section 13.6]).
i. Subjects will be classified in terms of their response to study treatment at Visit 10 (Week 14), and nonresponders in all groups will be prescribed sulfasalazine and/or hydroxychloroquine as rescue medication according to the local label of the prescribed drug(s) starting at Visit 10 (Week 14) (or as close as possible to this Visit), in addition to the assigned study treatment, background MTX, and concomitant folic acid or equivalent (see Section 6.13.3).
j. Joint assessor will be independent to the rest of the study team. An independent joint assessor, blinded to other study assessments as well as the dosing regimen, will be identified at each study site to perform the swollen and tender joint counts. To ensure consistent joint evaluation throughout the study, individual subjects should be evaluated by the same joint assessor for all study visits whenever possible.
k. The CRP test can be repeated once during the Screening Period to assess eligibility, provided results arrive prior to the randomization date. No extensions of the Screening Period will be granted for missing laboratory data unless this is due to central laboratory error (after Sponsor approval).
l. Adverse events and SAEs are reported from the signature of the ICF.
m. Required for females of childbearing potential only. The pregnancy test will consist of a serum test at Screening, and urine tests at the scheduled time points thereafter; may be repeated more frequently if required by local practices, IRB/IECs or local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.
n. Samples for INR, aPTT, and fibrinogen should be collected prior to all other blood samples.
o. Lipid panel includes total cholesterol, HDL, LDL, triglycerides, lipoprotein (a), apolipoproteins (ApoB, ApoA1, and ApoB:ApoA1 ratio), and adiponectin.
p. Cardiovascular risk panel includes NT-proBNP, BNP and homocysteine.

q. Hematology includes RBC, WBC with differential, hemoglobin, hematocrit, and platelet count.
r. If the Investigator considers Screening laboratory tests with exclusionary results to be due to laboratory error or a transient condition, these tests may be repeated once during the Screening Period for confirmation.
s. At Visit 1 (Screening), Visit 2 (Week 0), Visit 3 (Week 1), Visit 5 (Week 4), Visit 7 (Week 8), Visit 9 (Week 12), Visit 11 (Week 16), Visit 13 (Week 20), Visit 15 (Week 24), Visit SFU-2 (Week 30), and Visit SFU-3 (Week 44), subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the chemistry panel. The chemistry panel will include urea nitrogen, creatinine, fasting glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, and albumin.
t. Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.
u. Pharmacogenetic sample should only be collected after separate consent is signed. Blood sample for PG assessment is collected at Visit 2 (baseline). If the blood draw at baseline is missed, the sample should be taken at the next visit that a blood draw is already scheduled.
v. At each specified visit, subjects should be assessed for any injection site reactions that have occurred since the previous injection (see Section 7.6.3.5). The assessment of injection site reactions should take place prior to the next scheduled injection of study treatment.
w. Chest X-ray (both posteroanterior and lateral) need not be conducted if performed within 8 weeks prior to the date of Screening and films or images are available for review. Films or images available at Screening and collected during the study should be kept as source documents.
x. Not applicable if chest X-ray has been performed within 8 weeks prior to the EoT Visit and films or images are available for review.
y. In approximately 33% of subjects, additional blood samples will be collected periodically throughout the study (PK subpopulation). A detailed schedule of all blood sample collections for all subjects, including the PK subpopulation, is provided in Table 5.
z. Blood samples will be collected for analysis of ADAs to OKZ and any neutralizing antibodies to OKZ in plasma. Samples will be collected at the same time as the blood samples that are collected for measurement of OKZ concentrations.
aa. The ADA sample taken at Visit 2 will serve as a baseline.

Table 2 CL04041022 (CREDO 1) Schedule of Events for Sample-rich PK Subpopulation Only

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Windows (days)[c]																		
Relative to Baseline	**-28 to -1**	**±0**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**-**	**±7**	**±7**	**±7**
Relative to Visit 11 (Week 16)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**28±3**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 12 (Week 18)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±2**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 13 (Week 20)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±1**	**28±1**	**-**	**-**	**-**
Obtain informed consent, optional PK informed consent, optional PG informed consent	✓[d]																	
Subject number assigned via IWRS	✓																	
Determine eligibility	✓	✓																
Demography	✓																	
Medical history and current medical conditions	✓																	
Height	✓																	
Weight	✓	✓			✓		✓		✓			✓			✓	✓	✓	✓
Physical examination	✓[e]	✓[e]	✓	✓	✓	✓	✓	✓	✓[e]	✓	✓	✓	✓	✓	✓[e]	✓	✓	✓[e]
Vital signs[f]	✓	✓[g]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraceptive history/status	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant and prior medications/non-drug therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization		✓																

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Windows (days)[c]																		
Relative to Baseline	**-28 to -1**	**±0**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**-**	**±7**	**±7**	**±7**
Relative to Visit 11 (Week 16)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**28±3**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 12 (Week 18)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±2**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 13 (Week 20)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±1**	**28±1**	**-**	**-**	**-**
Study treatment allocation through IWRS		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Administer study treatment[h]		✓[i, j]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[i]	✓				
Prescribe rescue medication for nonresponders[k]										✓								
EFFICACY ASSESSMENTS																		
Patient Global Assessment of Disease Activity (VAS)		✓		✓	✓		✓		✓			✓			✓			
Patient Assessment of Pain (VAS)		✓		✓	✓		✓		✓			✓			✓			
HAQ-DI		✓		✓	✓		✓		✓			✓			✓			
SF-36, EQ-5D, FACIT-Fatigue, and WPS-RA		✓							✓						✓			
Joint counts (Independent Joint Assessment)[l]	✓	✓		✓	✓		✓		✓	✓		✓			✓			
Physician Global Assessment VAS		✓		✓	✓		✓		✓			✓			✓			
CRP	✓[m]	✓		✓	✓		✓		✓			✓			✓	✓	✓	
ESR		✓							✓						✓			

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Windows (days)[c]																		
Relative to Baseline	**-28 to -1**	**±0**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**-**	**±7**	**±7**	**±7**
Relative to Visit 11 (Week 16)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**28±3**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 12 (Week 18)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±2**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 13 (Week 20)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±1**	**28±1**	**-**	**-**	**-**
LABORATORY/SAFETY ASSESSMENTS																		
AEs/SAE[n]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IGRA	✓													✓				
HIV serology	✓																	
HBsAg, anti-HBs, anti-HBc, HCV Ab	✓																	
Pregnancy test[o]	✓	✓			✓		✓		✓		✓		✓		✓	✓	✓	✓
INR, aPTT, fibrinogen[p]		✓			✓				✓						✓			✓
Lipid panel (fasting)[q]		✓			✓				✓						✓			✓
CV risk panel[r]		✓			✓				✓						✓			✓
HbA_{1c}	✓																	
Hematology[s]	✓[t]	✓	✓		✓		✓		✓		✓		✓		✓		✓	✓
Chemistry panel[u]	✓[t]	✓	✓		✓		✓		✓		✓		✓		✓		✓	✓
RF and anti-CCP	✓														✓			
Urinalysis[v]	✓	✓							✓						✓			✓
ANA and anti dsDNA antibody		✓													✓			✓
PG		✓[w]																
Serum biomarkers related to targeted pathway		✓[x]	✓	✓	✓				✓						✓			

Assessments[a]		**Randomized Double-Blind Treatment Period**														**Safety Follow-Up Period**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15/EoT**	**SFU-1**	**SFU-2**	**SFU-3**
Week	**Screening**	**0/Baseline**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 (+2[b])**	**26 (+4[b])**	**30 (+8[b])**	**44 (+22[b])**
Visit Windows (days)[c]																		
Relative to Baseline	**-28 to -1**	**±0**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**-**	**±7**	**±7**	**±7**
Relative to Visit 11 (Week 16)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**28±3**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 12 (Week 18)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±2**	**-**	**-**	**-**	**-**	**-**
Relative to Visit 13 (Week 20)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**14±1**	**28±1**	**-**	**-**	**-**
Assess injection site reactions[y]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
TB risk questionnaires	✓						✓			✓					✓		✓	
Chest X-ray	✓[z]														✓[aa]			
12-lead ECG	✓	✓													✓			✓
PHARMACOKINETIC/IMMUNOGENICITY ASSESSMENTS																		
PK blood sample (sample-rich PK subpopulation)[bb]		✓--------✓----✓----✓					✓		✓	✓	✓		✓---✓------✓				✓	
ADAs[cc]		✓[dd]			✓		✓		✓				✓		✓		✓	✓

Abbreviations: ADA = antidrug antibody; AEs = adverse events; ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-CCP = anti-citrullinated protein antibody; anti-HBs = hepatitis B surface antibody; anti-HBc = total hepatitis B core antibody; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BP = blood pressure; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; CV = cardiovascular; dsDNA = double-stranded DNA; ECG = electrocardiogram; EoT = End of Treatment; EQ-5D = European Quality of Life – 5 Dimensions; ESR = erythrocyte sedimentation rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; GGT = gamma-glutamyl transferase; HAQ-DI = Health Assessment Questionnaire-Disability Index; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCV Ab = hepatitis C virus antibody; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; ICF = informed consent form; IEC = Independent Ethics Committee; IGRA = interferon-gamma release assay; INR = International Normalized Ratio; IRB = Institutional Review Board; IWRS = Interactive Web Response System; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide; PG = pharmacogenetic(s); PK = pharmacokinetic(s); PRO = patient-reported outcomes; RBC = red blood count; RF = rheumatoid factor; SAE = serious adverse event; SC = subcutaneous(ly); SDAI = Simplified Disease Activity Index; SF-36 = Short Form-36; TB = tuberculosis; WBC = white blood count; WPS-RA = Work Productivity Survey – Rheumatoid Arthritis; VAS = Visual Analog Scale.

Note: Data for the CDAI and SDAI endpoints will be derived from the relevant applicable efficacy assessments performed as per the above Schedule of Events.

a. As much as possible, the assessments to be performed at each study visit will be conducted in the standard order outlined in Section 5.4. At all post-randomization visits, the PRO questionnaires should be performed first, prior to any discussion between the subject and site staff.
b. The number of weeks (+2, +4, +8, or +22) after the last dose of the study treatment.
c. For subjects in the sample-rich PK subpopulation, Visit 13 (Week 20) should be scheduled to fall within 14 ± 2 days after Visit 12 (Week 18) and 28 ± 3 days after Visit 11 (Week 16). Visit 14 (Week 22) and Visit 15/EoT (Week 24) should be scheduled to fall within 14 ± 1 days and 28 ± 1 days, respectively, relative to study treatment administration at Visit 13 (Week 20). Refer to Sections 5.4 and 7.2 for more details regarding visit windows for the sample-rich PK subpopulation.
d. A separate ICF will be completed for the main study, PK subpopulation (optional), and PG (optional). Written informed consent must be obtained prior to performance of any protocol-specific procedures, including the discontinuation of any prohibited medications.
e. Complete physical examination (see Section 7.6.7.1).
f. Vital signs include temperature, heart rate, BP, and respiratory rate.
g. Blood pressure and pulse also need to be reassessed 1 and 2 hours postdose at Visit 2.
h. If desired, SC injections may be rotated among the thighs and abdomen.
i. Subjects in the sample-rich PK subpopulation should use the same SC injection site (either abdomen or thigh) to administer the study treatment at Visit 2 and Visit 13 unless otherwise medically indicated.
j. Subjects will remain at the study site for at least 2 hours after the injection at Visit 2 to be assessed for onset of any systemic injection reactions (See Section 7.6.3.2 and Appendix 6 [Section 13.6]).
k. Subjects will be classified in terms of their response to study treatment at Visit 10 (Week 14), and nonresponders in all groups will be prescribed sulfasalazine and/or hydroxychloroquine as rescue medication according to the local label of the prescribed drug(s) starting at Visit 10 (Week 14) (or as close as possible to this Visit), in addition to the assigned study treatment, background MTX, and concomitant folic acid or equivalent (see Section 6.13.3).
l. Joint assessor will be independent to the rest of the study team. An independent joint assessor, blinded to other study assessments as well as the dosing regimen, will be identified at each study site to perform the swollen and tender joint counts. To ensure consistent joint evaluation throughout the study, individual subjects should be evaluated by the same joint assessor for all study visits whenever possible.
m. The CRP test can be repeated once during the Screening Period to assess eligibility, provided results arrive prior to the randomization date. No extensions of the Screening Period will be granted for missing laboratory data unless this is due to central laboratory error (after Sponsor approval).
n. Adverse events and SAEs are reported from the signature of the ICF.
o. Required for females of childbearing potential only. The pregnancy test will consist of a serum test at Screening, and urine tests at the scheduled time points thereafter; may be repeated more frequently if required by local practices, IRB/IECs or local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected.
p. Samples for INR, aPTT, and fibrinogen should be collected prior to all other blood samples.
q. Lipid panel includes total cholesterol, HDL, LDL, triglycerides, lipoprotein (a), apolipoproteins (ApoB, ApoA1, and ApoB:ApoA1 ratio), and adiponectin.
r. Cardiovascular risk panel includes NT-proBNP, BNP and homocysteine.
s. Hematology includes RBC, WBC with differential, hemoglobin, hematocrit, and platelet count.
t. If the Investigator considers Screening laboratory tests with exclusionary results to be due to laboratory error or a transient condition, these tests may be repeated once during the Screening Period for confirmation.
u. At Visit 1 (Screening), Visit 2 (Week 0), Visit 3 (Week 1), Visit 5 (Week 4), Visit 7 (Week 8), Visit 9 (Week 12), Visit 11 (Week 16), Visit 13 (Week 20), Visit 15 (Week 24), Visit SFU-2 (Week 30), and Visit SFU-3 (Week 44), subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted) for the purpose of conducting the chemistry panel. The chemistry panel will include urea nitrogen, creatinine, fasting glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, and albumin.

v. Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.
w. Pharmacogenetic sample should only be collected after separate consent is signed. Blood sample for PG assessment is collected at Visit 2 (baseline). If the blood draw at baseline is missed, the sample should be taken at the next visit that a blood draw is already scheduled.
x. For subjects in the sample-rich PK subpopulation, biomarker samples will be collected from all subjects at Visit 2 (Week 0), 1 day after the first dose, Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 4), Visit 9 (Week 12), and Visit 15 (Week 24).
y. At each specified visit, subjects should be assessed for any injection site reactions that have occurred since the previous injection (see Section 7.6.3.5). The assessment of injection site reactions should take place prior to the next scheduled injection of study treatment.
z. Chest X-ray (both posteroanterior and lateral) need not be conducted if performed within 8 weeks prior to the date of Screening and films or images are available for review. Films or images available at Screening and collected during the study should be kept as source documents.
aa. Not applicable if chest X-ray has been performed within 8 weeks prior to the EoT Visit and films or images are available for review.
bb. Subjects in the sample-rich PK subpopulation will return to the study site for additional serial PK blood collections as follows: 1 day, 4+1 days, and 11±1 days after first dose at Week 0; 7±1 days after second dose at Week 2; 1 day, 4+1 days, 7±1 days, and 11±1 days after dosing at Week 20; and 7±1 days after dosing at Week 22. A detailed schedule of all blood sample collections for all subjects, including the sample-rich PK subpopulation, is provided in Table 5.
cc. Blood samples will be collected for analysis of ADAs to OKZ and any neutralizing antibodies to OKZ in plasma. Samples will be collected at the same time as the blood samples that are collected for measurement of OKZ concentrations.
dd. The ADA sample taken at Visit 2 will serve as a baseline.

5.2 Discussion of Study Design

Once subjects have successfully completed the 4-week Screening Period, a total of 420 subjects will be randomized in a 1:1:1 ratio (140 subjects per treatment group) to 1 of 3 treatment groups as follows:

1. OKZ 64 mg q4w: SC injection of OKZ 64 mg q4w (alternating with SC injection of placebo OKZ q4w to maintain blinding) + MTX.
2. OKZ 64 mg q2w: SC injection of OKZ 64 mg q2w + MTX.
3. Placebo: SC injection of placebo q2w + MTX.

This is a double-blind study; as the placebo differs in appearance from OKZ, study treatment will be prepared by an independent unblinded pharmacist or designee (e.g., nurse) and provided to blinded site staff in blinded syringes that are identical in appearance. The SC injections of OKZ and placebo will be administered every other week by blinded trained study staff. As noted above for treatment group No. 1, in order to maintain the blind, subjects randomized to receive OKZ q4w will receive placebo injections at the alternate q4w interval (e.g., Week 2, Week 6, etc.) at prespecified visits as described in Table 1 or Table 2 (as applicable).

Throughout the double-blind Treatment Period, all subjects will be required to remain on a stable dose of background MTX at 15 to 25 mg/week (or ≥10 mg/week if there is documented intolerance to higher doses) with a stable route of administration, and concomitant treatment with folic acid ≥5 mg per week or equivalent is required for all subjects. From Week 0 through Week 24, subjects will return to the study site at least every other week for response and safety assessments as per Table 1 or Table 2 (as applicable). Blood samples to assess OKZ concentrations in plasma will be collected periodically during the Treatment Period as per Table 5.

Subjects will be classified in terms of their response to study treatment at Week 14, with nonresponders defined as subjects from any treatment group who do not improve by at least 20% in both SJC and TJC (66-68 joint assessment). Starting at or as close as possible to Week 14, nonresponders in all groups will be administered sulfasalazine and/or hydroxychloroquine as rescue medication in addition to their assigned treatment (see Section 6.13.3).

The last dose of study treatment (OKZ or placebo) will take place at Week 22.

After completion of the 24-week double-blind Treatment Period, subjects will be offered the opportunity to enter the long-term OLE study. Subjects who do not consent to participate in

the OLE study will come to the EoT Visit 2 weeks after the last dose of the study treatment for scheduled assessments, after which they will then enter the Safety Follow-Up Period. During the Safety Follow-Up Period, subjects will return for visits +4, +8, and +22 weeks after the last dose of study treatment at Week 22 as per Table 1 or Table 2 (as applicable) (Visits SFU-1 [Week 26], SFU-2 [Week 30], and SFU-3 [Week 44], respectively).

Subjects who discontinue randomized study treatment early will adhere to the double-blind Treatment Period visit schedule outlined in Table 1 or Table 2 (as applicable), as if they were still receiving study treatment. In addition, all subjects who discontinue study treatment early will be required to attend the EoT Visit +2 weeks after the last dose of study treatment, as well as extended Safety Follow-Up assessments +4 weeks (Visit SFU-1), +8 weeks (Visit SFU-2), and +22 weeks (Visit SFU-3) after the last dose of study treatment.

Adverse events will be assessed throughout the study period and evaluated using the CTCAE version 4.0.

There will be ongoing monitoring of safety events, including laboratory findings, by R-Pharm and R-Pharm's designee. In addition, safety will be assessed throughout the study by an independent Data Safety Monitoring Board (DSMB) (see Section 7.6.4 for further details).

5.2.1 Cardiovascular Risk Assessment

The RA population is known to have an increased risk of CV events. In order to fully assess the CV risks associated with OKZ, the following approach will be used:

1. Potential major adverse cardiac events (MACE) will be adjudicated by an independent Cardiovascular Adjudication Committee (CVAC) according to a predefined charter. The charter will define the criteria, data, and source documentation required to adjudicate all MACE.
2. Baseline CV risks including individual risk factors (e.g., tobacco use, presence of hypertension, diabetes mellitus, and lipid profile) will be assessed.
3. Known CV risk factors will be monitored and assessed to detect any trends over long-term exposure.

Cardiovascular risk assessment data will be provided to the CVAC for use in review and adjudication of MACE (see Section 7.6.4.2).

5.2.2 Safety Follow-up Assessments

Given the long half-life of OKZ (approximately 31 days), all subjects will be followed up for approximately 5 OKZ half-lives (i.e., 22 weeks) after the final dose of study treatment.

For subjects remaining on randomized therapy until the last scheduled dose of study treatment at Visit 14 (Week 22) and not entering the OLE study, a full safety assessment will be performed at the EoT Visit (Visit 15 [Week 24]) and extended Safety Follow-Up procedures will be performed at visits scheduled +4, +12, and +22 weeks after the last dose of study treatment (i.e., Visits SFU-1 [Week 26], SFU-2 [Week 30], and SFU-3 [Week 44], respectively).

Subjects who discontinue randomized study treatment early (i.e., prior to Week 24) will adhere to the established double-blind Treatment Period visit schedule outlined in Table 1 or Table 2 (as applicable), as if they were still receiving study treatment. In addition, all subjects who discontinue study treatment early will have extended Safety Follow-Up assessments performed at the following time points:

- Full safety assessment 2 weeks after the last dose of study treatment (EoT Visit) (see Section 5.4.2)
- Safety Follow-Up Visit +4 weeks after the last dose of study treatment (Visit SFU-1) (see Section 5.4.3.1)
- Safety Follow-Up Visit +12 weeks after the last dose of study treatment (Visit SFU-2) (see Section 5.4.3.2)
- Safety Follow-Up Visit +22 weeks after the last dose of study treatment (Visit SFU-3) (see Section 5.4.3.3)

Depending on the timing of study treatment discontinuation, it is possible that the double-blind Treatment Period visits (Visits 2 through 15) may occur at the same time as the Safety Follow-Up Visits. In such cases, the study site staff should complete all study procedures required by both visits; if there are overlaps in the required laboratory tests, however, only one set of tests will be performed.

All subjects will be reminded of study contact information to report potential SAEs and are to inform the Investigator if they experience such events during the Safety Follow-Up Period.

5.3 Selection of Study Population

The study population will consist of a representative group of subjects of at least 18 years of age, fulfilling ACR 2010 revised classification criteria for RA for at least 12 weeks prior to

Screening. Eligible subjects are required to have active RA defined as ≥6 tender joints out of 68 and ≥6 swollen joints out of 66 at Screening and baseline, in combination with CRP above the upper limit of normal (ULN) at Screening. Subjects must have been on background MTX treatment at 15 to 25 mg/week (or ≥10 mg/week if there is documented intolerance to higher doses) for at least 12 weeks prior to Screening with a stable dose and route of administration for at least 6 weeks prior to Screening and have experienced an inadequate response (see Section 5.1 for definition of inadequate response to MTX) to treatment. Subjects will be maintained on a stable dose of MTX therapy throughout the study, and concomitant treatment with folic acid ≥5 mg per week or equivalent will be required for all subjects.

This is an international study and it is expected that subjects will be enrolled at approximately 50 sites across 4 countries. A total of 420 subjects will be randomized. Enrollment will stop as soon as the target number of randomized subjects is reached.

5.3.1 Inclusion Criteria

Subjects may be enrolled in the study only if they meet 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 RA classified by ACR/EULAR 2010 revised classification criteria for RA (Aletaha et al, 2010) for at least 12 weeks prior to Screening.
    - If the subject was diagnosed according to ACR 1987 criteria previously, the Investigator may classify the subject per ACR 2010 retrospectively, using available source data.
4. Inadequate response to treatment with oral, SC, or intramuscular (IM) MTX (see Section 5.1 for definition of inadequate response to MTX treatment) for at least 12 weeks prior to Screening at a dose of 15 to 25 mg/week (or ≥10 mg/week if intolerant to higher doses)
    - The dose and means of administering MTX 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:

a. ≥6 tender joints (68-joint count) at Screening and baseline; and

b. ≥6 swollen joints (66-joint count) at Screening and baseline; and

c. CRP above ULN at Screening based on the central laboratory results.

5.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be 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 are Steinbrocker class IV functional capacity (incapacitated, largely or wholly bed-ridden or confined to a wheelchair, with little or no self-care) (see Appendix 1 [Section 13.1])
3. Prior exposure to any licensed or investigational compound directly or indirectly targeting IL-6 or IL-6R (including tofacitinib or other Janus kinases and spleen tyrosine kinase [SYK] inhibitors)
4. Prior treatment with cell-depleting therapies, including anti-CD20 or investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, and anti-CD19)
5. Prior use of bDMARDs, with the following exception:
   - Subjects who discontinued TNFi therapy due to a reason other than lack of efficacy are allowed to enter the study (TNFi therapy 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). The use of TNFi therapy within the following windows prior to baseline is exclusionary:
     a. 4 weeks for etanercept
     b. 8 weeks for infliximab
     c. 10 weeks for adalimumab, certolizumab, and golimumab
6. Use of parenteral and/or intra-articular glucocorticoids within 4 weeks prior to baseline
7. Use of oral glucocorticoids greater than 10 mg/day prednisone (or equivalent), or change in dosage within 2 weeks prior to baseline

8. Prior documented history of no response to hydroxychloroquine and sulfasalazine
9. Prior use of cDMARDs (other than MTX) within the following windows prior to baseline (cDMARDs should not 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):
    a. 4 weeks for sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penicillamine, minocycline, or doxycycline
    b. 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 daily for at least 24 hours
    c. 24 weeks for cyclophosphamide
10. Vaccination with live vaccines in the 6 weeks prior to baseline or planned vaccination with live vaccines during the study
11. Participation in any other investigational drug study within 30 days or 5 times the terminal half-life of the investigational drug, whichever 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:
    a. Creatinine level ≥1.5 mg/dL (132 μmol/L) for females or ≥2.0 mg/dL (177 μmol/L) for males
    b. ALT or AST level ≥1.5× ULN
    c. Platelets $<100\times10^9$/L ($<100{,}000/mm^3$)
    d. White blood cell count $<3.5\times10^9$/L
    e. Neutrophil count $<2000\times10^6$/L ($<2000/mm^3$)

f. Hemoglobin level ≤80 g/L

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

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

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

18. Subjects with HIV infection

19. Subjects with:

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

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

    c. History of untreated latent TB infection (LTBI), regardless of IGRA result at Screening

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

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

            2. The subject has 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 (see Appendix 7 [Section 13.7]) (treatment with isoniazid for 6 months is not an appropriate prophylactic regime for this study and it should not be used); and

            3. The subject is willing to complete the entire course of recommended LTBI therapy (see Appendix 7 [Section 13.7]).

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

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

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

      2. The subject has 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 (see Appendix 7 [Section 13.7]) (treatment with isoniazid for 6 months is not an appropriate prophylactic regime for this study and it should not be used); and

      3. The subject is willing to complete the entire course of recommended LTBI therapy (see Appendix 7 [Section 13.7]).

   ii. If a subject with a positive IGRA result at Screening has documented evidence of completing treatment for LTBI with a treatment regime and treatment duration that are appropriate for this study, the subject may be enrolled without further prophylaxis if recommended by a certified TB specialist or pulmonologist who is 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 is suspected.

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

21. Subjects with any of the following CV conditions:

    a. Uncompensated congestive heart failure, or class III or IV heart failure defined by the New York Heart Association classification (The Criteria Committee of the New York Heart Association, 1994) as noted in Appendix 2 (see Section 13.2)

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

    c. History or presence of concurrent severe and/or uncontrolled CV disorder (including but not limited to acute coronary syndrome or stroke/transient ischemic attack in the

previous 3 months before Screening) that 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, 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 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 has 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 are pregnant, currently lactating, have lactated within the last 12 weeks, or who are planning to become pregnant during the study or within 6 months of last dose of study treatment

31. Female subjects of childbearing potential (unless permanent cessation of menstrual periods, determined retrospectively after a woman 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 documented serum follicle-stimulating hormone levels >40 mIU/mL and estradiol <20 pg/mL) who are not willing to use a highly effective method of contraception during the study and for at least 6 months after the last administration of study treatment

    OR

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

    Highly effective contraception is defined as:

    - Female sterilization surgery: hysterectomy, surgical bilateral oophorectomy (with or without hysterectomy), or tubal ligation at least 6 weeks prior to the first dose of study treatment
        - In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by documented follow-up hormone level assessment
    - Total abstinence if it is the preferred and constant lifestyle of the subject. Thus, periodic abstinence such as ovulation, symptothermal, postovulation, calendar methods, and withdrawal are 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 or contraindication to any component of the rescue medication (see Section 6.13.3)

34. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies

35. Subject's unwillingness or inability to follow the procedures outlined in the protocol

36. Other medical or psychiatric conditions or laboratory abnormalities that 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

5.3.3 Disease Diagnostic Criteria

Subjects must have a diagnosis of adult-onset RA classified by 2010 revised classification criteria for RA (Aletaha et al, 2010) for at least 12 weeks prior to Screening. Details of the ACR/EULAR 2010 criteria are provided in Appendix 3 (see Section 13.3). If the subject was previously diagnosed according to ACR 1987 criteria, the Investigator may classify the subject per ACR/EULAR 2010 retrospectively, using available source data.

5.3.4 Subject Restrictions

The following restrictions may affect a subject’s ability to participate in this study:

- Availability to attend visits according to the protocol within the allowed window period specified in Table 1 or Table 2 (as applicable)
- Concomitant medication restrictions as described in Section 6.13
- Fasting (water and concomitant medications are permitted) for at least 9 hours prior to certain visits which include routine laboratory assessments as defined in Section 5.4.

The Investigator (or designee) should review these restrictions with the subject during the Screening Period to determine any potential challenges in the subject’s ability to comply with the protocol. Subjects not able to comply with the above mentioned restrictions should not be enrolled into the study.

5.3.5 Premature Subject Withdrawal

All subjects are 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 occurs for any reason, the Investigator must make 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).

Subject will be completely withdrawn from study treatment and all assessments in the following cases:

- Withdrawal of informed consent
- Death of subject
- Subject lost to follow-up
  - Note: If the subject is lost to follow-up, the Investigator should attempt to contact the subject until the last scheduled Follow-Up visit at Week 44. The date of study termination for the subject is the date of last contact with subject.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. R-Pharm may retain and continue to use any data collected before such withdrawal of consent.

Investigators are strongly encouraged to discuss the withdrawal of a subject with R-Pharm or R-Pharm's designee in advance whenever possible.

Subjects who are withdrawn from the study will not be replaced.

5.4 Study Procedures

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject.

The timing for all study visits during the double-blind Treatment Period (Visit 3 [Week 1] through Visit 15 [Week 24]) is relative to baseline (Visit 2 [Week 0]). The timing for all study visits during the Safety Follow-Up Period (Visits SFU-1, SFU-2, and SFU-3) is relative to the last dose of study treatment (+4, +8, and +22 weeks, respectively).

As much as possible, subjects should be seen for all scheduled visits on the designated day. If a subject is unable to attend a scheduled visit on the designated day, the subject should be seen as closely as possible to the originally scheduled visit day.

The following visit windows are allowed (see Table 1 and Table 2), although their use should be avoided if possible:

- Visit 1 (Screening) and Visit 2 (baseline): ±0 days
- Visit 3 (Week 1): ±2 days
  - Subjects in the sample-rich PK subpopulation must adhere to a ±1-day visit window for Visit 3 (Week 1)
- Visits 4 through 15/EoT (Weeks 2 through 24): ±3 days
  - Subjects in the sample-rich PK subpopulation must adhere to a ±1-day visit window for Visit 4 (Week 2), Visit 5 (Week 4), Visit 14 (Week 22), and Visit 15/EoT (Week 24)
  - Additional restrictions for the sample-rich PK subpopulation are as follows:
    - Visit 13 (Week 20) should be scheduled to fall within 14 ± 2 days after Visit 12 (Week 18) and 28 ± 3 days after Visit 11 (Week 16).
    - Visit 14 (Week 22) should be scheduled to fall within 14 ± 1 days relative to study treatment administration at Visit 13 (Week 20)
    - Visit 15/EoT (Week 24) should be scheduled to fall within 28 ± 1 days relative to study treatment administration at Visit 13 (Week 20).
- Visits SFU-1, SFU-2, and SFU-3: ±7 days

A detailed discussion of the visit schedule and visit windows for the sample-rich PK subpopulation can be found in Section 7.2.

In all cases, there must be at least 1 week between each administration of the study. If a subject misses a visit and comes for an Unscheduled Visit, procedures for the assessment of safety and efficacy should be performed according to the most recent visit that was omitted. When a protocol required procedure cannot be performed, the Investigator will document in the source documents the reason for this and any corrective and preventive actions that he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team should be informed of these incidents in a timely fashion.

Subjects are required to fast for at least 9 hours (water and concomitant medications are permitted) prior to the following visits: Visit 1 (Screening), Visit 3 (Week 1), Visit 2 (Randomization, Week 0), Visit 5 (Week 4), Visit 7 (Week 8), Visit 9 (Week 12), Visit 11

(Week 16), Visit 13 (Week 20), Visit 15 (Week 24), Visit SFU-2 (Week 30), and Visit SFU-3 (Week 44).

The assessments to be performed at each study visit will be conducted in the standard order listed below. At all post-Screening visits, the PRO questionnaires should be performed first, prior to any discussion between the subject and site staff.

The standard order should be:

- All PRO questionnaires (prior to any discussion between the subject and site staff)
  - Patient Global Assessment of Disease Activity (Visual Analog Scale [VAS])
  - Patient Assessment of Pain (VAS)
  - HAQ-DI
  - SF-36
  - EQ-5D
  - FACIT-Fatigue
  - WPS-RA (this PRO is conducted by study site staff after the subject completes all other PROs)
- Joint counts (Independent Joint Assessment)
- Soliciting of AE information
- Physician Global Assessment (VAS)
- All other assessments

In the following sections, assessments are listed for each visit according to this order.

5.4.1 Double-blind Period: Visit 1 (Screening) through Visit 15 (Week 24)

5.4.1.1 Screening (Visit 1, Days -28 to -1)

A separate ICF is completed for the main study, PK subpopulation (optional), and PG study (optional). Written informed consent must be obtained prior to the performance of any protocol-specific procedures at Screening, including the discontinuation of any prohibited medications. The Investigator at each study site will ensure that each subject has been provided with full and adequate oral and written information about the nature, purpose, and available details of possible risks and benefits of the study.

Subjects must also be notified that they are free to discontinue from the study treatment or the whole study at any time. The Investigator will discuss with the subject the importance of participation in the study despite the discontinuation of study treatment. The subject should be given the opportunity to ask questions and allowed adequate time to consider the written information provided. The Investigator must retain the original, signed ICF for the study file. A copy of the signed ICF must be given to the subject. Once informed consent has been obtained, the subject's eligibility to enter the study will be verified in accordance with the inclusion and exclusion criteria (refer to Sections 5.3.1 and 5.3.2, respectively).

Enrollment will occur using an IWRS at Screening upon ICF signature. The IWRS will assign a unique subject number at Screening.

Screening may be conducted up to 28 days prior to randomization.

If the Investigator considers Screening laboratory tests with exclusionary results to be due to laboratory error or a transient condition, these tests may be repeated once during the Screening Period for confirmation. In addition, the CRP test can be repeated once during the Screening Period to assess eligibility, provided that the results arrive prior to the randomization date. No extensions of the Screening Period will be granted for missing laboratory data unless this is due to a central laboratory error.

Screen failure and re-screening are discussed in Section 5.4.4.

In addition to obtaining subject informed consent, the following assessments will be performed at Screening:

- Assign subject number via IWRS.
- Check eligibility criteria, including documenting of tender joints and diagnosis of RA.
- Record subject demographics.
- Record medical history.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record height and weight.
- Perform complete physical examination (see Section 7.6.7.1).
- Record vital signs (see Section 7.6.7.2).
- Administer TB risk questionnaire (see Section 7.6.9).

- Perform chest X-ray (see Section 7.6.7.5).
  - Chest X-ray need not be conducted if performed and evaluated within 8 weeks prior to Screening, and if the films or images are available and included in the subject's source documents.
- Perform joint counts (Independent Joint Assessment).
  - Joint assessor will be independent to the rest of the study team. An independent joint assessor, blinded to other study assessments as well as the dosing regimen, will be identified at each study site to perform the SJC and TJC. To ensure consistent joint evaluation throughout the study, individual subjects should be evaluated by the same joint assessor for all study visits whenever possible.
- Record all AEs from the time of ICF signature.
- Perform 12-lead electrocardiogram (ECG) (see Section 7.6.7.4).
- Perform IGRA as noted in Section 7.6.6.1. If results are indeterminate, the IGRA can be repeated once.
- Perform virology screen (HCV Ab, HBsAg, anti-HBs, anti-HBc, and HIV-1/HIV-2 antibody screen; see Section 7.6.6.1).
- Collect sample for serum pregnancy test.
  - This is required for females of childbearing potential only.
- Collect sample to measure CRP level.
  - The CRP test can be repeated once during the Screening Period to assess eligibility, provided results arrive prior to the randomization date. No extensions of the Screening Period will be granted for missing laboratory data unless this is due to central laboratory error.
- Collect samples for HbA_{1c} level, chemistry panel, and hematology assessments (see Section 7.6.6.1).
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
  - For subjects with abnormal laboratory values at Screening, 1 re-test is allowed during the 28-day Screening Period if the Investigator believes that exclusionary results are due to laboratory error or a transient, clinically non-significant condition.

- Collect samples for measurement of anti-CCP and RF.
- Perform urinalysis (see Section 7.6.6.1).

5.4.1.2 Randomization (Visit 2, Week 0)

The results of all Screening procedures must be available at or prior to the baseline visit (Visit 2) to determine eligibility for enrollment into the study. The Investigator must evaluate the results of laboratory tests performed at Screening to determine if any laboratory test results are outside the ranges specified in the eligibility criteria and joint counts should be reconfirmed before randomization; no exceptions to these requirements will be allowed.

If a subject meets all study eligibility criteria, the Investigator will randomize the subject via an IWRS; if not, then the subject should be recorded as a screen failure in the IWRS.

Baseline tests and procedures must be performed before administration of the first dose of study treatment.

The following assessments will be performed:

- Review eligibility criteria.
- Perform joint counts (Independent Joint Assessment).
- After confirmation that the subject has met all study entry criteria, randomize the eligible subject via IWRS to 1 of 3 treatment groups.
- Allocate study treatment through IWRS.
- Administer Patient Global Assessment of Disease Activity (VAS) (see Section 7.1.3).
- Administer Patient Assessment of Pain (VAS) (see Section 7.1.4).
- Administer HAQ-DI (see Section 7.1.10.1).
- Administer SF-36, EQ-5D, FACIT-Fatigue, and WPS-RA (see Section 7.1.10).
- Record AEs.
- Administer Physician Global Assessment (VAS, see Section 7.1.5).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.

- Perform complete physical examination (see Section 7.6.7.1).
- Record vital signs.
  - BP and pulse also need to be reassessed 1 and 2 hours postdose.
- Perform 12-lead ECG.
- Collect samples for international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen.
- Measure ESR (see Section 7.6.6.1).
- Collect sample to measure CRP level.
- Collect samples for lipid panel and CV risk panel (see Section 7.6.6.1).
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the lipid panel assessment.
- Collect samples for chemistry panel, hematology assessments, antinuclear antibodies (ANA), and double-stranded DNA (dsDNA) antibodies.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect sample for PG for subjects consented to participate in optional PG assessment (see Section 7.4).
- Collect sample for serum biomarkers related to targeted pathway (see Section 7.5).
  - Subjects who have consented in a separate, optional ICF to be included in the sample-rich PK subpopulation will return to study sites for the collection of an additional biomarker blood sample at approximately 24 ± 8 hours (1 day ± 8 hours) following Visit 2.
- Collect PK sample prior to the first dose of study treatment (see Table 5).
  - Subjects who have consented in a separate, optional ICF to be included in the sample-rich PK subpopulation will return to the study site for the collection of blood samples for PK assessments approximately 24 ± 8 hours (1 day ± 8 hours) and 96 + 24 hours (4 + 1 days) following Visit 2.

- Collect sample for analysis of ADAs.
  - The ADA sample taken at Visit 2 prior to the first dose of study treatment will serve as a baseline.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.
- Administer study treatment.
  - Subcutaneous OKZ 64 mg q4w, OKZ 64 mg q2w, or placebo will be administered by study site staff once all baseline evaluations are complete.
  - Subcutaneous injections may be rotated among the thighs and abdomen.
  - Subjects in the sample-rich PK subpopulation should use the same SC injection site (either abdomen or thigh) to administer the study treatment at Visit 2 and Visit 13 unless otherwise medically indicated.
  - All subjects will remain at the study site for at least 2 hours after the injection to be assessed for onset of any systemic injection reactions (see Section 7.6.3.2).

5.4.1.3 Visit 3 (Week 1)

The following assessments will be conducted at Visit 3:

- Record AEs and injection site reactions that have occurred since the previous visit.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect sample for serum biomarkers related to targeted pathway (for subjects included in the sample-rich PK subpopulation only).

- Collect PK sample (see Table 5).
  - Subjects in the sample-rich PK subpopulation will return to the study site for the collection an additional blood sample approximately 4 ± 1 days following Visit 3 (264 ± 24 hours [11 ± 1 days] relative to Visit 2).

5.4.1.4 Visit 4 (Week 2)

The following assessments will be conducted at Visit 4:

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.
- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect samples to measure CRP level.
- Collect sample for serum biomarkers related to targeted pathway (for subjects included in the sample-rich PK subpopulation only).
- Collect PK sample (see Table 5).
  - For subjects included in the sample-rich PK subpopulation, the PK sample at Visit 4 (Week 2) should be collected prior to study treatment administration (336 ± 24 hours [14 ± 1 days] relative to Visit 2).
  - Subjects in the sample-rich PK subpopulation will return to the study site for the collection an additional blood sample approximately 1 week following Visit 4 (504 ± 24 hours [21 ± 1 days] relative to Visit 2).
- Allocate study treatment through IWRS.

- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.5 Visit 5 (Week 4)

The following assessments will be conducted at Visit 5:

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.
- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect samples for INR, aPTT, and fibrinogen.
- Collect samples to measure CRP level.
- Collect samples for lipid panel and CV risk panel:
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the lipid panel assessment.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.

- Collect sample for serum biomarkers related to targeted pathway.
- Collect PK sample (see Table 5).
  - For subjects in the sample-rich PK subpopulation, the PK sample at Visit 5 (Week 4) should be collected prior to study treatment administration (672 ± 24 hours [28 ± 1 days] relative to Visit 2).
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.6 Visits 6 and 8 (Weeks 6 and 10)

The following assessments will be conducted at Visits 6 and 8:

- Record AEs and injection site reactions that have occurred since the previous visit.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.7 Visit 7 (Week 8)

The following assessments will be conducted at Visit 7:

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.
- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire.
- Record weight.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect samples to measure CRP level.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect PK sample (see Table 5).
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.8 Visit 9 (Week 12)

The following assessments will be conducted at Visit 9:

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Administer SF-36, EQ-5D, FACIT-Fatigue, and WPS-RA.
- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.
- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Perform complete physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect samples for INR, aPTT, and fibrinogen.
- Measure ESR (see Section 7.6.6.1).
- Collect samples to measure CRP level.
- Collect samples for lipid panel and CV risk panel.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the lipid panel assessment.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect blood sample for serum biomarkers related to targeted pathway.
- Collect PK sample (see Table 5).

- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.9 Visit 10 (Week 14)

At Week 14, subjects will be classified as responders or nonresponders as per the definitions detailed in Section 5.2. This will be entered into the IWRS as described in a separate IWRS Manual. Subjects who are classified as nonresponders are prescribed 1 or both of 2 commercially available DMARDs as rescue medication in addition to the study treatment (see Section 6.13.3).

The following assessments will also be conducted at Visit 10:

- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect PK sample (see Table 5).
- Allocate study treatment through IWRS.
- Prescribe rescue medication for nonresponders.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.

- All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.10 Visit 11 (Week 16)

The following assessments will be conducted at Visit 11:

- Record AEs and injection site reactions that have occurred since the previous visit.
- Record details of contraceptive history/status.
- Record concomitant medications and significant concomitant non-drug therapies.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect PK sample (see Table 5).
- Perform urine pregnancy test for females of childbearing potential only.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.11 Visit 12 (Week 18)

The following assessments will be conducted at Visit 12:

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.

- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect sample to measure CRP level.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.12 Visit 13 (Week 20)

For subjects in the sample-rich PK subpopulation, Visit 13 (Week 20) should be scheduled to fall within 14 ± 2 days after Visit 12 (Week 18) and 28 ± 3 days after Visit 11 (Week 16).

The following assessments will be conducted at Visit 13:

- Record AEs and injection site reactions that have occurred since the previous visit.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect sample for analysis of ADAs.

- Collect PK sample (see Table 5).
  - Subjects in the sample-rich PK subpopulation will return to the study site for the collection of additional blood samples approximately 24 ± 8 hours (1 day ± 8 hours), 96 + 24 hours (4 + 1 days), 168 ± 24 hours (7 ± 1 days), and 264 ± 24 hours (11 ± 1 days) following Visit 13.
- Perform urine pregnancy test for females of childbearing potential only.
- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - Subjects in the sample-rich PK subpopulation should use the same SC injection site (either abdomen or thigh) to administer the study treatment at Visit 2 and Visit 13 unless otherwise medically indicated.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.1.13 Visit 14 (Week 22)

For subjects in the sample-rich PK subpopulation, Visit 14 (Week 22) should be scheduled to fall within 14 ± 1 days relative to study treatment administration at Visit 13 (Week 20).

The following assessments will be conducted at Visit 14:

- Record AEs and injection site reactions that have occurred since the previous visit.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Perform IGRA. If results are indeterminate, the IGRA can be repeated once.
- Collect PK sample (see Table 5).
  - For subjects included in the sample-rich PK subpopulation, the PK sample at Visit 14 (Week 22) should be collected prior to study treatment administration (336 ± 24 hours [14 ± 1 days] relative to Visit 13).

- Subjects in the sample-rich PK subpopulation will return to the study site for collection of an additional blood sample approximately 7 ± 1 days following Visit 14 (504 ± 24 hours [21 ± 1 days] relative to Visit 13).

- Allocate study treatment through IWRS.
- Administer study treatment.
  - If desired, SC injections may be rotated among the thighs and abdomen.
  - All subjects will remain at the study site for 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

5.4.2 Visit 15/End of Treatment (2 Weeks after the Last Dose of the Study Treatment)/(Week 24)

The EoT Visit (Visit 15) will be performed 2 weeks after the last dose of study treatment for subjects who choose not to enter the OLE (Week 24) and for subjects who discontinue study treatment prematurely.

For subjects in the sample-rich PK subpopulation, Visit 15/EoT (Week 24) should be scheduled to fall within 28 ± 1 days relative to study treatment administration at Visit 13 (Week 20)

The following assessments will be performed at the EoT Visit for all subjects:

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Administer SF-36, EQ-5D, FACIT-Fatigue, and WPS-RA.
- Perform joint counts (Independent Joint Assessment).
- Record AEs and injection site reactions that have occurred since the previous visit.
- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire.
- Record weight.

- Perform complete physical examination (see Section 7.6.7.1).
- Record vital signs.
- Perform chest X-ray.
  - Chest X-ray need not be conducted if performed and evaluated within 8 weeks prior to the EoT Visit, and if the films or images are available and included in the subject's source documents.
- Perform 12-lead ECG.
- Collect samples for INR, aPTT, and fibrinogen.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for lipid panel and CV risk panel.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the lipid panel assessment.
- Collect sample for serum biomarkers related to targeted pathway.
- Collect samples for chemistry panel, hematology, ANAs, and dsDNA antibodies assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect samples for measurement of anti-CCP and RF.
- Collect PK sample (see Table 5).
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.

5.4.3 Safety Follow-up: Visits SFU-1, SFU-2, and SFU-3

5.4.3.1 Visit SFU-1 (Week 26 or 4 Weeks after the Last Dose of the Study Treatment)

The following assessments will be conducted 4 weeks after the last dose of the study treatment:

- Record AEs.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect sample to measure CRP level.
- Perform urine pregnancy test for females of childbearing potential only.

5.4.3.2 Visit SFU-2 (Week 30 or 8 Weeks after the Last Dose of the Study Treatment)

The following assessments will be conducted 8 weeks after the last dose of the study treatment:

- Record AEs.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire.
- Record weight.
- Perform partial physical examination (see Section 7.6.7.1).
- Record vital signs.
- Collect sample to measure CRP level.
- Collect samples for chemistry panel and hematology assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.

- Collect PK sample (see Table 5).
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.

5.4.3.3 Visit SFU-3 (Week 44 or 22 Weeks after the Last Dose of the Study Treatment)

The following assessments will be conducted 22 weeks after the last dose of the study treatment:

- Record AEs.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Perform complete physical examination (see Section 7.6.7.1).
- Record vital signs.
- Perform 12-lead ECG.
- Collect samples for INR, aPTT, and fibrinogen.
- Collect samples for lipid panel and CV risk panel.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the lipid panel assessment.
- Collect samples for chemistry panel, hematology, ANAs, and dsDNA antibodies assessments.
  - Subjects must attend study sites after fasting (water and concomitant medications are permitted) for at least 9 hours for the purpose of conducting the chemistry panel.
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.

5.4.4 Screen Failure and Re-Screening

Subjects who are considered to be screen failures must be recorded as such in the IWRS.

At a minimum, the demographics and eligibility criteria (i.e., inclusion and/or exclusion criteria) are to be documented in the eCRF for all screen failures.

Subjects who are screen failures may be re-screened with prior approval of R-Pharm or R-Pharm's designee. The IWRS will assign a new subject number and all Screening assessments must be repeated (see Section 5.4.1.1), with the following exceptions:

- Chest X-ray does not need to be repeated if a chest X-ray was performed within 8 weeks prior to the date of re-screening and films or images are available for review.
- For subjects with documented LTBI who have completed at least 30 days of TB prophylaxis, the IGRA does not need to be repeated at the re-screening visit.

5.4.5 Unscheduled Visit

It is at the Investigator's discretion to initiate an Unscheduled Visit, if deemed necessary by the Investigator for the subject's safety and well-being. At this visit, any of the assessments from the Schedule of Events may be performed dependent on the presenting reason. When a protocol-required procedure cannot be performed at the scheduled time the Investigator will document in the source documents the reason for this and any corrective and preventive actions that he/she has taken to ensure that normal processes are adhered to as soon as possible. R-Pharm's designee should be informed of these incidents in a timely fashion.

6. STUDY TREATMENTS

6.1 Study Treatment Administered

Study Treatment

All eligible subjects will be randomly assigned in a 1:1:1 ratio to the OKZ and placebo treatment groups described in Section 5.2. A detailed description of the study treatment (OKZ and placebo) is provided in Section 6.2.

Background Therapy

All subjects will continue to receive their prior background therapy (MTX) during the study.

As per inclusion criterion No. 4 (see Section 5.3.1), subjects must have been treated with MTX at a dose of 15 to 25 mg/week (or ≥10 mg/week if there is documented intolerance to higher doses) for at least 12 weeks prior to Screening with a stable dose and an unchanged mode of administration (oral, SC, or IM) for at least 6 weeks prior to Screening.

The dose of background MTX should remain unchanged throughout the study and may be adjusted only for safety reasons according to Investigator discretion. If the Investigator judges that the dose of MTX must be adjusted for safety reasons, this may only be done once during the study. If needed, a reduction in the MTX dose may be made according to the guidelines in Appendix 4 (see Section 13.4).

Rescue Medication

Starting at Week 14, nonresponders will be assigned rescue medication (sulfasalazine and/or hydroxychloroquine) in addition to their assigned study treatment (see Section 6.13.3).

6.2 Identity of Study Treatment

Olokizumab and placebo (sodium chloride 0.9%) will be supplied by R-Pharm or its designee.

6.2.1 Olokizumab

Olokizumab is a humanized (CDR-grafted) mAb of the IgG4/kappa isotype with the serine in the heavy chain hinge region being replaced with a proline residue. The OKZ drug substance consists of a preparation of purified recombinant humanized mAb (CDP6038; L04041) presented as a solution of 160 mg/mL OKZ in 30 mM histidine hydrochloride, 60 mM sodium chloride, 200 mM sorbitol, and 0.03% polysorbate 80 at pH 5.6.

Olokizumab is presented as a sterile solution for SC injection in a 2 mL clear Type I glass vial, containing a target fill volume of 1.1 mL (for withdrawal of not less than 0.8 mL) or a target fill volume of 0.5 mL (for withdrawal of not less than 0.4 mL) of OKZ drug substance, at a concentration of 160 mg/mL. The aqueous formulation buffer contains 30 mM histidine hydrochloride, 60 mM sodium chloride, 200 mM sorbitol, and 0.03% polysorbate 80, at pH 5.6. The vial is closed with a chlorobutyl stopper and sealed with an aluminum seal with a polypropylene flip-off cap.

Olokizumab is to be administered SC and will be presented in a blinded syringe so that it appears identical to placebo.

An outline of the components and composition of the OKZ drug product is presented in Table 3.

Table 3 Components and Composition of OKZ (CDP6038; L04041) Drug Product

Ingredient	Quantity (per mL)	Function
OKZ drug substance	160.000 mg	Active ingredient
Sodium chloride[a]	3.51 mg	Tonicity
Polysorbate 80[a]	0.3 mg	Stabilizer
Histidine hydrochoride[a]	6.29 mg	Buffer
Sorbitol[a]	36.434 mg	Stabilizer
Water for injection[a]	qs to 1.0 mL	Solvent

Abbreviations: OKZ = Olokizumab; qs = quantum satis (sufficient quantity).
a. Added during the drug substance manufacturing process.

6.2.2 Placebo

Placebo (sodium chloride 0.9%) will be supplied in polypropylene plastic ampoules of 10 mL, packed in cardboard cartons to contain 10 ampoules. The placebo will contain no active pharmaceutical ingredients.

Placebo will be administered in a blinded manner. As the placebo differs in appearance from OKZ, it will be prepared by independent unblinded site staff and provided to the blinded site staff in blinded syringes with the same appearance as syringes containing OKZ. Subjects randomized to the placebo group will be administered placebo by study site staff via SC injection q2w. In order to maintain the blind, subjects randomized to receive OKZ q4w will receive placebo at the alternate q4w interval (e.g., Week 2, Week 6, etc.).

6.3 Packaging and Labeling

Study treatment will be supplied in cartons containing either 1 vial of OKZ or 10 ampoules of placebo. Study treatment will be packaged and labeled according to Good Manufacturing Practices and all applicable local country regulations with information on the study protocol number, drug identification, storage conditions, and dosage information.

6.4 Storage

The Investigator or designee is responsible for the safekeeping and correct storage of the study treatment (OKZ and placebo) at the study site.

Olokizumab will be shipped and stored refrigerated at +2°C to 8°C (36°F to 46°F) in a secure, temperature-controlled refrigerator. Placebo must be stored as per the manufacturer's requirement. Both OKZ and placebo will be supplied centrally by a clinical supplies vendor. In order to maintain the blind, the study treatment will be stored separately at the study site in a secure area inaccessible to blinded study staff. Please refer to the Pharmacy Manual for additional details on storage requirements.

6.5 Method of Assigning Subjects to Treatment Group

Once a subject's eligibility has been confirmed, subjects will be randomized in a 1:1:1 ratio by blinded study staff using IWRS (an automated web randomization system). The IWRS will then allocate treatment group and assign study treatment. This system will also manage drug supply management and visit dispensation. Blinded study staff will request study treatment assignment via IWRS for all subsequent treatment study visits. Further details on the IWRS and requirements for each study visit can be found in the separate IWRS manual.

6.6 Study Treatment Accountability

The unblinded pharmacist or an unblinded delegate at the study site is responsible for maintaining an adequate record of the receipt and distribution of study treatment. The drug accountability records must be kept current, available for monitoring by the unblinded monitor, and available for inspection at any time. Study treatment materials should be kept in a secured location that is inaccessible to blinded staff. The used study treatment must be discarded as a biohazard, and the handling, disposal and destruction details will be detailed in the Pharmacy Manual.

The Investigator is responsible for maintaining an adequate record of study treatment administration and study treatment compliance.

Detailed instructions on drug accountability are provided in the Pharmacy Manual.

6.7 Treatment Compliance

The Investigator should promote compliance by stating that compliance is necessary for the subject's safety and the validity of the study. The prescribed dosage, timing, and mode of administration may not be changed. All dates and times of study treatment administration and any departures from the intended regimen must be recorded on the appropriate eCRF page.

An unblinded monitor will review the pharmacy records at each study site including the drug dispensing records on which the pharmacist or designated person should record all study treatment released for subject use. The unblinded monitor will compare the dispensing record and vials with the individual subject's identifiers and visit schedule to confirm that the subject received the correct treatment and dose, and that the dosing schedule is correct. Errors that are identified will be communicated to the study site personnel to ensure that the errors are not repeated. Unblinded staff will be notified in an unblinded manner, and blinded staff will be notified in a blinded manner. The monitor's report will include details of any missed doses, errors in dose, treatment errors, or scheduling errors and the associated explanations. All supplies and pharmacy documentation must be made available throughout the study for the monitor to review.

It will not be necessary for study sites to retain used syringes. Compliance with study treatment is defined as the administration of the study treatment conforming to no less than 90% of the dose regimen specified in this protocol since study treatment will be administered by the Investigator or study personnel. Any subject who deviates from the dosing schedule or misses any scheduled treatment should be reported to R-Pharm and/or R-Pharm's designee promptly for determination of possible schedule adjustments and continued eligibility (in the event of multiple missed doses). If a subject is found to be persistently noncompliant, R-Pharm and/or R-Pharm's designee, in conjunction with the Investigator, will make a decision as to whether the subject should be discontinued from the study treatment (see Section 6.11).

6.8 Preparation and Administration of Study Treatment

Both OKZ and placebo will be prepared in syringes of 0.4 mL for SC injection by an independent unblinded pharmacist or designee. In order to maintain the blind, the SC syringes will be blinded as per the instructions in the Pharmacy Manual prior to dispensing, in a manner that both treatments will be identical in appearance. Sites should arrange to prepare the SC syringes in a way timed to avoid exceeding the stipulated stability time of the prepared product. The solution may remain in the syringe for a maximum of 4 hours prior to its administration. The prepared SC syringes should be warmed at room temperature prior to handing over to the blinded study staff for study treatment administration.

At randomization, subjects will be randomly assigned to receive 1 of the 3 treatments discussed in Section 5.2. Qualified blinded study staff will administer 1 SC injection (0.4 mL of OKZ or placebo) q2w or q4w at the relevant time points as per Table 1 or Table 2 (as applicable). If desired, SC injections may be rotated among the thighs and abdomen (for subjects in the sample-rich PK subpopulation, the same SC injection site [either abdomen or thigh] should be used to administer the study treatment at Visits 2 and 13 unless otherwise medically indicated). All subjects will remain at the study site for at least 30 minutes following each administration of study treatment (or 2 hours after Visit 2 [Week 0]) to be assessed for onset of any systemic injection reactions (see Section 7.6.3.2).

The date, time, and location of the SC injection should be recorded in the eCRF. The Investigator should also record in the eCRF whether or not the full dose was administered.

There must be at least 1 week between each administration of the study treatment (refer to Section 5.4 for the visit windows allowed for each study visit).

Further detailed instructions on study treatment preparation and handling are provided in the Pharmacy Manual.

6.9 Selection and Timing of Dose for Each Subject

Subjects will be assigned study treatment (see Section 5.2) as discussed in Section 6.5.

6.10 Dose Adjustments

Dose adjustments for OKZ/placebo are not allowed in this study. For guidelines regarding dose reduction of MTX refer to Appendix 4 (see Section 13.4).

6.11 Discontinuation of Study Treatment

All subjects are free to discontinue study treatment at any time, for any reason, specified or unspecified, and without prejudice to further treatment.

If discontinuation of study treatment occurs for any reason, the Investigator must make every effort to determine the primary reason for a subject's discontinuation of study treatment and record this information on the source documents and appropriate eCRF.

In all cases, if a subject discontinues from the study treatment, all efforts will be made to have them continue in the study; all visits and scheduled procedures (see Section 5.4) should be performed unless the subject also withdraws informed consent to participate in the study (see Section 5.3.5). If a subject who discontinues study treatment does not return for a scheduled visit, every effort should be made to contact the subject. In all circumstances, every effort should be made to document subject outcome.

6.11.1 Temporary Discontinuation of Study Treatment

The following laboratory abnormalities require prompt retesting following the reporting of the initial abnormal result (within 72 hours for abnormal LFTs and within 5 days for all other abnormal results):

- Any single ALT and/or AST elevation >3× ULN, regardless of total bilirubin (repeat laboratory testing must include total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase [GGT], INR, alkaline phosphatase, creatine phosphokinase, and hematology assessment)
- Neutrophil count $<1000\times10^6$/L (<1000 /mm^3)
- Lymphocyte count $<500\times10^6$/L (<500 /mm^3)
- Platelet count <100,000 platelets/mm^3
- Any single hemoglobin value <8.0 g/dL or one that drops ≥20 g/L (2 g/dL) below baseline

The next dose of study treatment will be held/interrupted if:

- Results from the repeat laboratory testing are not available at the time of the next scheduled dose
- ALT and/or AST remain >3× ULN with total bilirubin ≤2× ULN after repeat laboratory testing and there are no symptoms consistent with hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash). The Investigator may consider restarting study treatment only after discussion with the R-Pharm Medical Advisor or designee (see also Appendix 4 [Section 13.4]).

Clinically significant laboratory abnormalities should be re-tested and followed until resolution, stabilization, or return to baseline values, and the Investigator should contact the Medical Monitor for guidance regarding restarting the study treatment.

Study treatment should not be administered to subjects with active or clinically significant infections.

Temporary interruption of study treatment should also be considered if, at the discretion of the Investigator, it is necessary for safety reasons (e.g., negative trends during laboratory monitoring or remaining abnormalities after retesting which do not require premature discontinuation of the study treatment but could be harmful for the patient according to the Investigator's judgement, or other clinically significant newly diagnosed co-morbidity that

requires additional assessments for clarification of the diagnosis, and the severity of which could worsen if study treatment is continued).

The Investigator should contact the Medical Monitor for guidance regarding restarting study treatment.

6.11.2 Permanent Discontinuation of Study Treatment

The criteria for enrollment are to be followed explicitly.

If a subject who does not meet enrollment criteria is inadvertently enrolled, R-Pharm or R-Pharm's designee must be informed immediately and the subject must immediately and permanently discontinue study treatment.

If, in the opinion of the Investigator, a subject is consistently noncompliant with the protocol in regards to study procedures, use of concomitant medications, or dosing with the study treatment, the case will be reviewed by R-Pharm on a case-by-case basis and noncompliant subjects can be discontinued from study treatment.

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

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

- Investigator decides that the subject should be discontinued from study treatment. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the study treatment is to be discontinued, appropriate measures are to be taken, and R-Pharm or R-Pharm`s designee is to be notified.
- Subject is unwilling to continue the study treatment. If the subject discontinues from the study treatment, the Investigator should inquire about the reason for discontinuing.
- Subject presents with any of the following elevated LFTs (see also Appendix 4 [Section 13.4]):
  - ALT or 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 presents 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 and decreased ≥20 g/L (2 g/dL) below Screening value
  - Creatinine value >2× ULN
- Subject has confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
- R-Pharm, a regulatory agency, or an ethical committee stops the study for any reason.
- Administration of a live vaccine during the study.
- Subject has a GI perforation.
- Subject has a severe or life-threatening infection that requires hospitalization (which is also an SAE; see Section 7.6.2).
  - Confirmed active TB is an SAE (see Section 7.6.2), must be recorded on the relevant AE pages of the eCRF, and will be provided to R-Pharm in accordance with SAE reporting requirements as outlined in Section 7.6.5.2. As with all SAEs, periodic follow-up reports should be completed according to protocol requirements (i.e., through 22 weeks of safety follow-up) until such time as the TB infection resolves.

6.12 Blinding

This is a randomized, double-blind, placebo-controlled study. Access to randomization codes will be restricted. The treatment each subject will receive will not be disclosed to the blinded site staff, including the Investigator, study coordinator, subject, R-Pharm, or R-Pharm's designee. Since the study treatments are distinguishable, they will be prepared by the unblinded pharmacist (or their unblinded designee) out of sight of the subject and any blinded study team members and provided to blinded site staff in blinded syringes that are identical in appearance. The study site staff will be trained in methods that must be followed

and documented to prevent unblinding. Guidance on specific blinding procedures will be provided in the Study Reference Manual. The treatment codes will be held by the IWRS. Only the unblinded pharmacist (or their unblinded designee) or dedicated unblinded staff who are not directly involved in subject management will be aware of the randomized drug assignment. The storage and preparation of study treatment will be at a secured location that is not accessible to blinded investigational staff.

Additional measures to ensure that both Investigators and subjects remain blinded to study treatment include the following:

- Joint assessments will be made by an independent assessor, blinded to both the dosing regimen and all other study assessments.
- Laboratory results for CRP and ESR samples collected during the Treatment Period will not be available to blinded study site staff. As ESR will be tested locally, the testing will be performed, reviewed, and registered by unblinded study site staff who are not responsible for managing subjects.
- Certain efficacy assessments (ACR20, ACR50, ACR70, DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI) will not be calculated by the Investigator during the course of the study, but will instead be computed in the statistical database for analysis purposes.

All blinding procedures should be respected.

Members of the independent DSMB will separately review safety data during the study. In the event that ongoing safety monitoring uncovers an issue that needs to be addressed by unblinding at the treatment group level, only members of the DSMB are permitted to conduct additional analysis of the safety data.

6.12.1 Unblinding

The process for unblinding will be handled through the IWRS, which will be accessible at all times. Investigators are strongly discouraged from requesting the blind be broken for an individual subject, unless there is a subject safety issue that requires unblinding and would change subject management. Any site that breaks the blind under inappropriate circumstances may be asked to discontinue its participation in the study. If the blind is broken, it may be broken for only the subject in question. The Investigator should make every effort to discuss the subject's case with R-Pharm (or its designee) prior to unblinding.

R-Pharm and/or R-Pharm's designee must be notified immediately if a subject and/or Investigator is unblinded during the course of the study. Pertinent information regarding the

circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents and eCRFs.

6.13 Prior and Concomitant Treatments

Concomitant treatment with MTX is detailed in Section 6.1. Specifically, at the discretion of the Investigator, the dose of MTX can be reduced once during the study for safety reasons according to the guidelines in Appendix 4 (see Section 13.4).

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

Other specifically allowed medications are discussed in Section 6.13.2.

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

A caution regarding cytochrome P (CYP) and transporter proteins is discussed in Section 6.13.1.

Table 4 Prohibited Medications

Treatment	Restriction
cDMARDs other than MTX	• Treatment with cDMARDs other than MTX is prohibited during the entire study, with the exception of sulfasalazine and/or hydroxychloroquine, which are permitted as rescue medication for nonresponders starting at Week 14 as described in Section 6.13.3 • Prior use of cDMARDs other than MTX within the following windows prior to baseline is exclusionary (cDMARDs 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): o 4 weeks for sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penicillamine, minocycline, or doxycycline. o 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 three 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) is prohibited during the entire study and their use prior to Screening is 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), is prohibited during the entire study and their use prior to Screening is exclusionary. • Treatment with bDMARDs (including TNFi therapy) is prohibited during the entire study and their use prior to Screening is exclusionary, with the following exception: o Subjects who discontinued TNFi therapy due to a reason other than lack of efficacy are allowed to enter the study (TNFi therapy 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). The use of TNFi therapy within the following windows prior to baseline is exclusionary: - 4 weeks for etanercept - 8 weeks for infliximab - 10 weeks for adalimumab, certolizumab, and golimumab

Treatment	Restriction
Corticosteroids	• Treatment with an oral glucocorticoids greater than 10 mg/day prednisone or equivalent or a change in dosage within 2 weeks prior to baseline is exclusionary. • Use of parenteral glucocorticoids within 4 weeks prior to baseline is exclusionary. Use of parenteral glucocorticoids is strongly discouraged during the entire study, but limited use is allowed in the following circumstance: o No more than 2 joints may be injected at or after Week 14 after all study assessments for this time point are performed. The injection must not 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 are prohibited during the entire study with the following exceptions: o Stable doses of NSAIDs are permitted during the study if the subject has received stable doses for ≥2 weeks prior to baseline (see Section 6.13.2). Doses of NSAIDs must be kept constant throughout the entire study unless the Investigator changes the dose for safety reasons. Switching of NSAIDs is not allowed. However, if the subject has an AE that requires discontinuation of the NSAID, an alternative NSAID may be initiated per the local label (if not contraindicated). • Aspirin use at daily doses up to 325 mg is permitted if indicated for CV protection. At this dose, aspirin will not be considered an NSAID.
Analgesics	• Analgesics, including opioids, are prohibited during the entire study with the following exception (see Section 6.13.2): o Paracetamol/acetaminophen: Maximum 2000 mg per day (maximum 1000 mg per dose). Paracetamol/acetaminophen are not to be taken within 24 hours prior to joint assessment, including baseline assessment.
Hyaluronic acid	• Intra-articular hyaluronic acid is prohibited during the entire study and its use within 4 weeks prior to baseline is exclusionary.
Vaccination	• Live vaccinations are 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.

6.13.1 Olokizumab Potential Impact on Cytochrome P and Transporter Pathways

Based on nonclinical data (refer to the most recent version of the Investigator's Brochure), it is possible that OKZ may reverse IL-6-mediated inhibition of CYP or transporter pathways such as CYP1A1/2, 2B6, 2C9, 3A4/5, and 2C19 and sodium/taurocholate co-transporting polypeptide. If CYP or transporter activity is de-suppressed (i.e., increased to any relevant

extent), this may result in decreased level of drugs eliminated by these pathways. As such, OKZ may have clinical relevance for CYP substrates with narrow therapeutic index and for which a change in effectiveness may be undesirable. Investigators are advised to monitor substrates with a narrow therapeutic index (as noted in their respective package inserts/drug labels) and to contact the Medical Monitor to discuss any potential concerns about concomitant medications.

6.13.2 Allowed Medications

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

- Inhaled corticosteroids
- Topical corticosteroids
- Oral corticosteroids
  - Doses of ≤10 mg/day of prednisone or equivalent are permitted as long as the dose was not changed within the 2 weeks prior to baseline; dose adjustments are not permitted during the study unless the Investigator changes the dose for safety reasons.
- Intra-articular corticosteroids
  - No more than 2 joints may be injected during the study at or after Week 14, after all study assessments for this time point are performed. The cumulative dose for both injections must 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 should be omitted from all subsequent joint assessments (see Sections 7.1.2, 7.1.6, and 7.1.7).
- NSAIDs
  - The subject must have received a stable dose for ≥2 weeks prior to baseline, and the dose must be kept constant throughout the entire study unless the Investigator changes the dose for safety reasons.
- Analgesic treatment with paracetamol/acetaminophen is 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 is lower. Paracetamol/acetaminophen are not to be taken within 24 hours prior to joint assessment, including baseline assessment.

6.13.3 Rescue Medication Starting at Week 14

Subjects will be classified in terms of their response to study treatment at Week 14, with nonresponders defined as all subjects who do not improve by at least 20% in both SJC and TJC (66-68 joint assessment). Nonresponders in all groups will be 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 are:

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

Nonresponders at Week 14 will remain blinded to their assigned treatment. Rescue medication will be 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 receive rescue medication, periodic safety evaluations for toxicity resulting from sulfasalazine and/or hydroxychloroquine should be undertaken as per the drug label and local guidelines.

6.14 Medical Treatment for Subjects after End of Study

After completion of the 24-week double-blind Treatment Period, subjects will either roll over into the long-term OLE study or enter the Safety Follow-Up Period. For subjects who complete the study without entering the OLE and for all subjects who discontinue study treatment prematurely, it is the responsibility of the Investigator to choose adequate treatment.

7. EFFICACY, SAFETY, PHARMACOKINETIC, AND HEALTH OUTCOME ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 American College of Rheumatology 20%/50%/70% Response Criteria

ACR20/ACR50/ACR70 will not be calculated by the Investigator during the course of the study, but will be computed in the statistical database for analysis purposes.

The number of subjects who achieve an ACR20, ACR50, or ACR70 response at various time points will be calculated for OKZ and placebo. The calculations are based on a ≥20%, ≥50%, and ≥70% improvement from baseline in the SJC assessed in 66 joints and in the TJC assessed in 68 joints; and a ≥20%, ≥50%, and ≥70% improvement from baseline in at least 3 of the 5 remaining core set measures:

- Patient Global Assessment of Disease Activity (VAS).
- Patient Assessment of Pain (VAS).
- HAQ-DI.
- Physician Global Assessment (VAS).
- Level of acute phase reactant (CRP or ESR, using level of CRP in this study).

7.1.2 66-68 Joint Assessment

The 66-68 joint assessment evaluates 66 joints for swelling and 68 joints for tenderness and pain on motion. The hip joints can be assessed for tenderness, but not for swelling. The following joints are included:

- Temporomandibular, sternoclavicular, acromioclavicular, shoulders, elbows, wrists, interphalangeal (IP) on digit 1, distal interphalangeals on digits 2 to 5, proximal interphalangeals (PIP) on digits 2 to 5, metacarpophalangeal (MCP) on digits 1 to 5, hips (tenderness only), knees, ankles and tarsus; metatarsals, IP on toe 1, PIP on toes 2 to 5, and metatarsophalangeals (MTP) on toes 1 to 5.

As noted in Table 1 and Table 2, the joint assessor will be independent to the rest of the study team. An independent joint assessor, blinded to other study assessments as well as the dosing regimen, will be identified at each study site to perform the SJC and TJC. To ensure consistent joint evaluation throughout the study, individual subjects should be evaluated by the same joint assessor for all study visits, whenever possible.

Artificial, missing, and ankylosed joints are excluded from both tenderness and swelling assessments. If joints are missing or not able to be assessed, the number of joints will be weighted by the actual number of assessable joints, and the missing or not assessable joints should be marked as "not assessed" for all subsequent joint assessments for the remainder of the study. If a subject receives intra-articular corticosteroids at or after Week 14 (see Section 6.13), any treated joints should be omitted from all subsequent joint assessments and should be rated with their pre-injection status for the remainder of the study.

7.1.3 Patient Global Assessment of Disease Activity (Visual Analog Scale)

Subjects will assess the overall disease activity by responding to the following:

- Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing, using a 100 mm VAS where 0 is "very well" and 100 is "very poorly."

7.1.4 Patient Assessment of Pain (Visual Analog Scale)

Subjects will rate their level of short-term arthritis pain by responding to the question:

- How much pain are you experiencing because of your illness AT THIS TIME? Place a vertical (I) mark on the line to indicate the severity of the pain, using a 100 mm VAS where 0 is "no pain" and 100 is "severe pain."

7.1.5 Physician Global Assessment (Visual Analog Scale)

The Investigator will rate the overall status of the subject for the day of the visit, with respect to RA signs and symptoms and the functional capacity of the subject. The Investigator will respond to the following:

- Mark an X on the line below to indicate disease activity (independent of the patient's self-assessment). A 100 mm VAS will be used, where 0 is "no disease activity" and 100 is "maximal disease activity."

7.1.6 Disease Activity Score 28-Joint Count (C-Reactive Protein)

The DAS28 (CRP) will not be calculated by the Investigator during the course of the study, but will be computed in the statistical database for analysis purposes. The DAS28 (CRP) will be kept blinded after Screening.

The DAS28 (CRP) will be calculated using the SJC (28 joints), TJC (28 joints), CRP level, and the Patient Global Assessment of Disease Activity (VAS) (in mm) according to the following formula:

DAS28 (CRP) = 0.56 × √(TJC) + 0.28 × √(SJC) + 0.36 × lognat (CRP + 1) + 0.014 × Patient Global Assessment of Disease Activity (VAS) + 0.96

The 28 joints evaluated for the SJC and TJC are as follows:

- Shoulders, elbows, wrists, IP on digit 1, PIP on digits 2 to 5, MCP on digits 1 to 5, and knees.

Details of the joint assessment process are provided in Section 7.1.2.

7.1.7 Disease Activity Score 28-Joint Count (Erythrocyte Sedimentation Rate)

The DAS28 (ESR) will not be calculated by the Investigator during the course of the study, but will be computed in the statistical database for analysis purposes. The DAS28 (ESR) will be kept blinded after Screening.

The DAS28 (ESR) will be calculated using the SJC (28 joints), TJC (28 joints), ESR (mm/hour), and the Patient Global Assessment of Disease Activity (VAS) (in mm) according to the following formula:

DAS28 (ESR) = 0.56 × √(TJC) + 0.28 × √(SJC) + 0.70 × lognat (ESR) + 0.014 × Patient Global Assessment of Disease Activity (VAS)

The 28 joints evaluated for the SJC and TJC are as follows:

- Shoulders, elbows, wrists, IP on digit 1, PIP on digits 2 to 5, MCP on digits 1 to 5, and knees.

Details of the joint assessment process are provided in Section 7.1.2.

7.1.8 Simplified Disease Activity Index

The SDAI will not be calculated by the Investigator during the course of the study, but will be computed in the statistical database for analysis purposes.

The SDAI will be calculated using the SJC (28 joints), TJC (28 joints), CRP (mg/dL), the Patient Global Assessment of Disease Activity (VAS) (in cm), and the Physician Global Assessment (VAS) (in cm) according to the following formula:

SDAI = SJC + TJC + Patient Global Assessment of Disease Activity (VAS) + Physician Global Assessment (VAS) + CRP

7.1.9 Clinical Disease Activity Index

The CDAI will not be calculated by the Investigator during the course of the study, but will be computed in the statistical database for analysis purposes.

The CDAI will be calculated using the SJC (28 joints), TJC (28 joints), the Patient Global Assessment of Disease Activity (VAS) (in cm), and the Physician Global Assessment (VAS) (in cm) according to the following formula:

CDAI = SJC + TJC + Patient Global Assessment of Disease Activity (VAS) + Physician Global Assessment (VAS).

7.1.10 Health Assessments and Patient-Reported Outcomes

The PROs that will be utilized for efficacy assessments are discussed in this section.

7.1.10.1 Health Assessment Quiestionnaire – Disability Index

The HAQ-DI is a patient-reported questionnaire that provides an assessment of the impact of the disease and its treatment on physical function. The HAQ-DI assesses the degree of difficulty experienced in 8 domains of daily living activities using 20 questions. The domains are dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities, and each domain (activity) consists of 2 or 3 items. For each question, the level of difficulty is scored from 0 to 3 where 0 = without any difficulty, 1 = with some difficulty, 2 = much difficulty, and 3 = unable to do. Each category is given a score by taking the maximum score of each question (i.e., question in each category with the highest score for that category).

If the maximum score is 0 or 1, but a device related to that category is used, or help from another person is provided for the category, then the category score is increased to 2. If the category score is already a 2 (or above), the score in that category remains 2 with or without any aids or device use. If the subject does not provide an answer for any questions within a category, no score will be provided for that category. The HAQ-DI will be calculated by dividing the sum of the category scores by the number of categories with at least 1 question answered. If fewer than 6 categories have responses, no disability score will be calculated.

The HAQ-DI will also include patient assessments of pain and health on a scale of 0 to 100.

7.1.10.2 Short Form-36

The SF-36 health survey is a patient-reported survey of health; it is commonly used in health economics as a variable in the quality-adjusted life year (QALY) calculation to determine the cost-effectiveness of a health treatment. The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to

100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

The 8 domains of the SF-36 are as follows:

- Vitality
- Physical functioning
- Bodily pain
- General health perceptions
- Physical role functioning
- Emotional role functioning
- Social role functioning
- Mental health

7.1.10.3 European Quality of Life – 5 Dimensions

The conceptual basis of the EQ-5D is the holistic view of health, which includes the medical definition and the fundamental importance of independent physical, emotional, and social functioning. The concept of health in EQ-5D also encompasses both positive aspects (well-being) and negative aspects (illness).

The EQ-5D consists of a questionnaire and a VAS and is a self-rated health status. The EQ-5D records the subject's perceptions of their own current overall health, and can be used to monitor changes with time. The self-assessment questionnaire is a description of the 5 dimensions (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The subject is asked to grade their own current level of function in each dimension into 1 of 5 degrees of disability (extreme, severe, moderate, slight, or none). The combination of these with the conditions "death" and "unconscious" enables description of 3127 different health states. Each health state can be ranked and transformed as a single score called the utility.

The EQ-5D health states may be converted into a single summary index by applying a formula that attaches values to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e., state 11111). Value sets have been derived for EQ-5D in several countries using the European

Quality of Life-5 Dimensions Visual Analog Scale (EQ-5D VAS) valuation technique or the time trade-off valuation technique.

7.1.10.4 Work Productivity Survey – Rheumatoid Arthritis

The WPS-RA measures the impact of RA and treatment on subject productivity within and outside the home during the previous month. It contains 9 questions addressing employment status, productivity within and outside the home, and daily activities. One item of the WPS-RA addresses current labor market participation. This is a strong indicator of work ability because not working implies complete loss of paid productivity. There are also normative and comparative data available on employment status. Two items capture self-reported work absences due to arthritis, and 2 items capture the same concept but applied to non-paid work. These are separated into full and partial days (i.e., days of work missed and days with productivity reduced by at least half). Additional items capture the respondent's estimate of the extent to which arthritis has interfered with the subject's work productivity (paid and non-paid) on a scale of 0 to 10, the number of days in the last month outside help was hired because of arthritis, and the number of days in the last month family, social, or leisure activities were missed because of arthritis.

7.1.10.5 Functional Assessment of Chronic Illness Therapy – Fatigue Scale

FACIT-Fatigue is a 13-item tool that measures an individual's level of fatigue during their usual daily activities during the most recent week. The level of fatigue is measured on a 4-point Likert scale.

The sum of the scoring (total score) will be used for the statistical evaluation. If an item is not scored, the total score will be set to missing.

7.2 Pharmacokinetics

Blood samples (approximately 2 mL/sample) for determination of OKZ concentrations in plasma will be collected from all subjects. Olokizumab in plasma will be assessed as follows:

- All subjects: Blood samples for measurement of OKZ concentrations will be collected at each time a blood sample is taken for the determination of ADAs (ADA/PK matched subjects), with the exception of the final Safety Follow-Up Visit (Visit SFU-3). However, OKZ concentrations will only be analyzed and reported for subjects who have a confirmed positive ADA response in any of the postdose samples.
- PK subpopulation: In approximately one third (33%) of subjects (approximately 140 consenting subjects), additional blood samples will be collected periodically

throughout the study for analysis of OKZ in plasma to be included in a population PK assessment.

- Sample-rich PK subpopulation: In at least 42 of the 140 consenting subjects in the PK subpopulation, additional ICF will be consented and serial blood samples will be collected following the first dose of study treatment (Week 0) and over a 4-week period at steady state (Weeks 20 through 24) to reach appropriate number of the enrolled subjects for further analysis of PK parameters . Olokizumab PK parameters will be determined by using noncompartmental analysis in subjects randomized to OKZ following single (Week 0) and multiple dose (Week 20) administration, as appropriate.
  - The IWRS will be constructed to select consenting subjects to be included in the PK subpopulation in a blinded fashion based on the group to which they are randomized.
  - Subjects in the sample-rich PK subpopulation should use the same SC injection site (either abdomen or thigh) to administer the study treatment at Visit 2 and Visit 13 unless otherwise medically indicated.

All PK samples will be collected at the sampling times shown in Table 5. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. Details on sample processing, handling, shipment, and storage are provided in a separate Laboratory Manual. Tubes and preprinted labels will be provided by the central laboratory to the study sites.

The following information will be captured for blood PK sample collection in each subject's eCRF:

- Patient number and initials
- Date and time of study treatment administration for the last 2 visits preceding the PK sample collection
- Date and time of the blood PK sample collection
- Date and time of study treatment administration on visit day of PK blood collection
- Sampling problems will be noted in the Comments section

The number of subjects included in the PK subpopulation is considered to be sufficient to describe individual OKZ PK following serial sample collections after the first dose of OKZ and at steady state, and to allow for assessment of accumulation after multiple-dose administration. Protocol deviations or events affecting the PK results may interfere with PK assessments. Prior to unblinding, deviations and other events will be reviewed to assess if

they may affect PK. If a subject or sample has a deviation or event that may affect the interpretation of PK, the subject or sample may be excluded from the PK population or the PK analysis.

Assuming an approximately 15% rate of discontinuation after the first dose, serial OKZ concentrations in PK sample-rich sub-population are expected to be available for approximately 13 to 14 subjects per OKZ treatment group following the dose on Day 1 and approximately 11 to 12 subjects per OKZ treatment group at steady state. In addition, the PK data obtained in the PK subpopulation combined with the sparse sample collection (up to 12 scheduled samples in all enrolled subjects receiving OKZ as shown in Table 5) will provide a sample-rich analysis dataset for population PK assessment to be utilized either in a study-specific PK analysis and/or in combination with PK data from other studies.

Table 5 Sample Collection for PK, ADA, and Biomarker Assessments

Visit	Week	Dose	Time relative to OKZ dose[a]	Dedicated PK sample collection in PK subpopulation (approximately 140 subjects)		PK and ADA sample collection	Biomarker sample collection
				Sample-rich PK subpopulation (N≈42)	Remaining subjects (N≈98)	All subjects[b] (N=420)	Sample-rich PK subpopulation (N≈42)
2	0	X	Immediately prior to first dose at Visit 2 (Day 0)[c]	X (±0 days)	X (±0 days)	X (±0 days)	X (±0 days)
			24 h postdose	X (±8 hours)			X (±8 hours)
			96 h postdose (Day 4)	X (+1 day)			
3	1		168 h postdose (Day 7)	X (±1 day)	X (±2 days)		X (±1 day)
			264 h postdose (Day 11)	X (±1 day)			
4	2	X	336 h postdose (Day 14)	X (±1 day) Collected prior to the next dose	X (±3 days)		X (±1 day)
			504 h postdose (Day 21)	X (±1 day)			
5	4	X	672 h postdose (Day 28)	X (±1 day) Collected prior to the next dose	X (±3 days)	X (±3 days)	X (±1 day)
7	8	X	predose	X (±3 days)	X (±3 days)	X (±3 days)	
9	12	X	predose	X (±3 days)	X (±3 days)	X(±3 days)	X (±1 day)
10	14	X	predose	X (±3 days)	X (±3 days)		
11	16	X	predose	X (±3 days)	X (±3 days)		
13	20	X	Immediately prior to dose at Visit 13 (Day 0)[c,d]	X (±3 days)	X (±3 days)	X (±3 days)	
			24 h postdose (Day 1)	X (±8 hours)			
			96 h postdose (Day 4)	X (+1 day)			
			168 h postdose (Day 7)	X (±1 day)			
			264 h postdose (Day 11)	X (±1 day)			

Visit	Week	Dose	Time relative to OKZ dose[a]	Dedicated PK sample collection in PK subpopulation (approximately 140 subjects)		PK and ADA sample collection	Biomarker sample collection
				Sample-rich PK subpopulation (N≈42)	Remaining subjects (N≈98)	All subjects[b] (N=420)	Sample-rich PK subpopulation (N≈42)
14	22	X	336 h postdose (Day 14)[d]	X (±1 day) Collected prior to the next dose	X (±3 days)		
			504 h postdose (Day 21)	X (±1 day)			
15	24		672 h postdose (Day 28)[d]	X[e] (±1 day)	X[e] (±3 days)	X[e] (±3 days)	X[e] (±1 day)
SFU-2	30 (+8[f])		n/a	X (±7 days)	X (±7 days)	X (±7 days)	
SFU-3	44 (+22[f])		n/a			X[g] (±7 days)	
Total number of samples collected for OKZ analysis				21	12	7	n/a
Volume of blood collected for OKZ analysis				42 mL	24 mL	14 mL	n/a

Abbreviations: ADA = antidrug antibody; n/a = not applicable OKZ = olokizumab; OLE = open-label extension; PK = pharmacokinetic(s).

a. The time relative to OKZ dose is for serial sample collections in the sample-rich PK subpopulation only.

b. Blood samples for measurement of OKZ concentrations will be collected at each time a blood sample is taken for the determination of ADAs. Olokizumab concentrations for subjects who are not part of the PK subpopulation will only be determined for subjects who have a confirmed positive ADA response in any of the postdose samples. In case of a confirmed positive ADA response at any time postdose during the Treatment Period, all PK samples collected for the subject will be analyzed.

c. In this table, the date of Visit 2 and Visit 13 for the overall study will be considered Day 0 for the purpose of collecting PK samples. Day 0 is defined as such for both series of PK sampling (beginning on Visit 2 and Visit 13). Subjects in the sample-rich PK subpopulation should use the same SC injection site (either abdomen or thigh) to administer the study treatment at Visit 2 and Visit 13 unless otherwise medically indicated.

d. For subjects in the sample-rich PK subpopulation only, Visit 13 (Week 20) should be scheduled to fall within 14 ± 2 days after Visit 12 (Week 18) and 28 ± 3 days after Visit 11 (Week 16), and Visit 14 (Week 22) and Visit 15/EoT (Week 24) should be scheduled to fall within 14 ± 1 days and 28 ± 1 days, respectively, relative to study treatment administration at Visit 13 (Week 20).

e. For subjects rolling over into the OLE study, the PK sample must be collected prior to the first dose of study treatment in the OLE study.

f. For subjects who discontinue study treatment prior to the final scheduled dose, Visits SFU-2 and SFU-3 will occur +8 and +22 weeks, respectively, after the last dose of study treatment.

g. At Visit SFU-3, blood samples will be collected for ADA analysis only; PK samples will not be collected.

Plasma will be analyzed, using appropriate bioanalytical methods, by R-Pharm or R-Pharm's designee for determination of OKZ concentrations. Full details of the analytical method used will be described in a separate bioanalytical report. Only samples from the subgroup of subjects receiving OKZ who consented to have samples taken for population PK analysis and/or serial PK analysis are initially scheduled to be analyzed. Samples from subjects receiving OKZ and not part of the planned PK analyses will only be analyzed in the case of a confirmed positive ADA response (see Section 7.3). If formation of ADAs is observed in any sample for a given subject, all OKZ PK samples will be analyzed for this subject. Samples from placebo subjects will not be analyzed.

Samples must be within the known stability of OKZ at the time of receipt by the bioanalytical laboratory to be analyzed.

Details on sample processing, handling, shipment, and storage are provided in a separate Laboratory Manual.

7.3 Immunogenicity

Immunogenicity will be assessed by evaluating the impact of ADAs on subject safety, efficacy, and PK of OKZ. Blood samples for analysis of the incidence and titer of antibodies to OKZ and the incidence of any neutralizing antibodies to OKZ in plasma will be collected at the times shown in Table 1, Table 2, and Table 5. The ADA sample taken at Visit 2 will serve as a baseline.

The actual sample collection date and exact time will be entered on the Immunogenicity Blood Collection eCRF page. Sampling problems will be noted in the Comments section of the eCRF. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. A Laboratory Manual will be provided to the Investigator with detailed information on sample collection, handling, and shipment of the ADA samples. Tubes and preprinted labels will be provided by the central laboratory to the study sites.

Antidrug antibody samples from all subjects who received OKZ will be analyzed, using appropriately validated methods, by R-Pharm or R-Pharm's designee. Samples will initially be screened for antibodies. A confirmation assay will be used to confirm the positive status for samples that scored potentially positive by the Screening assay. In confirmed positive samples, the relative titer of the antibody will be determined as well as whether the confirmed positive sample represents a neutralizing antibody.

Samples collected from subjects who received placebo will not be analyzed to determine ADA formation against OKZ, unless warranted by unexpected study results.

7.4 Pharmacogenetics

The following PG endpoints are exploratory and are not intended to be used for regulatory judgments pertaining to the safety or efficacy of the investigational drug. However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of new genomic biomarkers.

This study includes an optional exploratory PG assessment which requires signature of a separate informed consent if the subject agrees to participate. The identity of the subject will not be revealed. It is required as part of this protocol that the Investigator presents these options to the subject.

Exploratory PG studies are planned as a part of this study with the objectives of identifying inherited genetic factors that may (1) predict response to treatment with OKZ, (2) predict relative susceptibility to drug-drug interactions, (3) predict genetic predisposition to side effects, or (4) be related to RA and also predict response to treatment with OKZ. R-Pharm hopes to develop a better understanding of how subjects with RA respond to OKZ.

At all study sites, one optional blood sample will be collected in subjects for PG assessment at Visit 2 (baseline) after a separate PG ICF has been signed as indicated in Table 1 and Table 2. If the blood draw at baseline is missed, the sample should be taken at the next visit that a blood draw is already scheduled.

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment. The actual sample collection date must be entered on the Central Laboratory Assessment eCRF page.

Any DNA derived from the sample that remains after analysis may be stored for up to 15 years to address scientific questions related to OKZ or RA.

7.5 Serum biomarkers related to targeted pathway

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. This search for biomarkers of disease and drug response will involve an integrated molecular approach examining genetic and serum protein profiles. These exploratory assessments aim to identify potential markers of response and/or loss of response, and to characterize molecular mechanisms of treatment with OKZ.

Blood samples for biomarker analysis will be collected at the times shown in Table 1 or Table 2 (as applicable) and Table 5.

Any biomarker samples may be stored for up to 20 years (depending on local regulations) to research scientific questions related to OKZ, RA and related diseases with a potential involvement of IL-6. The material can be destroyed on subject's request at any time. Details on the collections, handling and shipment of the samples to the central laboratory will be provided to Investigators in the Laboratory Manual.

Any results from these exploratory biomarker assessments will be reported separately. Serum biomarkers related to systemic inflammation, bone and joint metabolism, and CV risk will be measured. The final selection of analytes will be driven by assay availability, new information from the public domain, results obtained in other OKZ clinical studies, as well as by hypotheses generated by other exploratory biomarker assessments. In addition, selected markers exploring the effect of OKZ treatment on co-morbidities may be assessed. At all study sites, blood samples will be collected for soluble serum markers pre-dose at the scheduled time points as indicated in Table 1 or Table 2 (as applicable). Samples should then be processed and shipped as detailed in the Laboratory Manual. The actual sample collection date will be entered on the corresponding eCRF page. Sampling problems will be noted in the Comments section of the eCRF.

7.6 Safety

Safety assessments will consist of monitoring and recording all AEs, including SAEs, nonserious AESIs, and pregnancies; measurement of safety laboratory assessments; measurement of vital signs, ECGs, physical examinations; and other tests that are deemed critical to the safety evaluation of the study in all subjects who receive at least 1 dose of study treatment. As discussed in Section 7.6.2.3, any pregnancy that occurs while a subject is enrolled in the study will also be monitored and reported according to the appropriate regulations.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious and nonserious that caused the subject to discontinue before completing the study. Any AE, including any AE still ongoing at the end of the study, should be followed until it has resolved, it has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. If no follow-up is provided, the Investigator must provide a justification.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical study records throughout the study. Further routine medical assessments in addition to those specified in Table 1 and Table 2 may take place during the study as clinically indicated (e.g., chest X-rays to investigate lung lesions, ECG, etc).

Safety measures in this study include, but are not limited to SAEs, AEs, vital signs, body weight, and laboratory evaluations, and if required, this information must be present in the AE/SAE report made by the Investigator.

7.6.1 Adverse Events

For the purposes of this study, an AE will be defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any of the following:

- Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
  - If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis (or signs or symptoms if a diagnosis is not possible) and is not a clinically significant worsening from the baseline laboratory parameter, it should be documented accordingly without being reported as a separate laboratory AE.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).

The Investigator is responsible for recording all AEs observed during the study from the time the subject signs the ICF. All AEs are recorded throughout the study until the last visit of the subject. The Investigator is responsible for the appropriate medical care of the subjects during the entire study.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE. The Investigator is required to assess causality as described below. For AEs with a causal relationship to the study treatment, follow-up by the Investigator is required until the event has resolved, it has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

Severity

The severity of AEs will be characterized according to the CTCAE grades and definitions summarized in Table 6.

Table 6 CTCAE Grades and Corresponding AE Severity

CTCAE Grade	Corresponding AE Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Abbreviations: ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

Causality Assessment

The Investigator is responsible for making an assessment of the causal relationship between the study treatment and the AE. Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment. The causal relationship between the study treatment and the AE must be characterized as "related" or "not related." The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of the study treatment.
- Course of the event, considering especially the effects of dose reduction, discontinuation of the study treatment, or reintroduction of the study treatment.
- Known association of the event with the study treatment, or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

The Investigator should report the relatedness of each event based on the most likely causal relationship, and the study site staff is responsible for obtaining any missing information.

7.6.1.1 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all subject evaluation time points. Examples of nondirective questions from the Investigator to the subject include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

7.6.2 Serious Adverse Events

An SAE experience or reaction is any untoward medical occurrence (whether considered to be related to study treatment or not) that at any dose:

- Results in death
- Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Other medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the other serious outcomes listed in the definition above.
  - Examples of such events are blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization.
  - Confirmed cases of active TB should be recorded and reported as SAEs.
  - Potential hepatotoxicity events that fulfill any of the following criteria should be recorded and reported as SAEs:
    - ALT >3× ULN and total bilirubin >2× ULN
    - ALT >8× ULN at any time, regardless of total bilirubin or accompanying symptoms
    - ALT >5× ULN for ≥2 weeks, regardless of total bilirubin or accompanying symptoms
    - ALT >3× ULN, accompanied by symptoms consistent with hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash)

Any AE that results in an unplanned hospitalization or prolonged hospitalization should be documented and reported as an SAE. The following hospitalization scenarios are examples of events not considered to be SAEs:

- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study treatment.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the subject's general condition.

Any SAEs occurring after a subject has received the last dose of study treatment will be collected and reported to R-Pharm's designee through the end of the Safety Follow-Up Period (i.e., for a period of 22 weeks after the last dose of study treatment), regardless of the Investigator's opinion of causality. The Investigator must also inform participating subjects of the need to inform the Investigator of any SAE that occurs within this period. Any SAE with a start date after the Safety Follow-Up Period is not required to be reported unless the Investigator thinks that the event may be related to either the study treatment, study treatment administration, or a protocol procedure.

All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to the study treatment, must be recorded on the SAE page in the eCRF and immediately reported to R-Pharm's designee. This includes death attributed to progression of RA.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the description of event on the SAE page in the eCRF. Generally, only 1 such event leading to death should be reported.

The use of the term "**sudden death**" as the description of an event should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting,

"**unexplained death**" should be recorded on the SAE page as the description of event in the eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

7.6.2.1 Lack of Efficacy or Worsening of Rheumatoid Arthritis

Medical occurrences or symptoms of deterioration that are anticipated as part of RA should be recorded as an AE if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of RA on the AEs eCRF page, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated RA"). Events that are clearly consistent with the expected pattern of progression of the underlying disease, as determined by the Investigator, should not be recorded as AEs; these data will be captured as efficacy assessment data only. Every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is an AE or due to disease progression, it should be reported as an AE.

Any worsening of RA that meets the criteria for seriousness should be reported as an SAE.

7.6.2.2 Overdose

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects. Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF. All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the AEs eCRF page.

7.6.2.3 Reporting and Follow-Up Requirements for Pregnancies

Pregnancies in Female Subjects

A serum pregnancy test will be conducted on all females of childbearing potential at Screening, and urine pregnancy tests will be conducted thereafter as presented in the Schedule of Events (Table 1 or Table 2 [as applicable]).

If a subject becomes pregnant after the administration of any study treatment, R-Pharm and/or R-Pharm's designee should be informed immediately. Study treatment should be discontinued as soon as the pregnancy is known and the following should be completed:

- The subject should immediately discontinue further administration of study treatment.
- The subject should return for an EoT Visit.

- All scheduled safety assessments must be performed unless contraindicated by pregnancy (harmful to fetus) or the subject withdraws informed consent.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives. The pregnancy should be followed-up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Full details will be recorded on a Pregnancy Report eCRF and submitted via the Electronic Data Capture (EDC) system, and reporting details will be detailed in the study manual. The Investigator will update the Pregnancy Report eCRF with additional information as soon as the outcome of the pregnancy is known.

If the outcome of the pregnancy is an SAE then this must be additionally reported as an SAE on the appropriate eCRF page.

Pregnancies in Female Partners of Male Subjects

Male subjects will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study and up to 3 months after the subject received the last injection of study treatment. A Pregnancy Report eCRF should be completed by the Investigator within 1 working day after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to the study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in co-operation with the treating physician and/or obstetrician.

7.6.3 Adverse Events of Special Interest

The following safety concerns were identified as AESIs based upon either the safety data available to date for OKZ (refer to the most recent version of the Investigator's Brochure) or drug class-related events for a biologic IL-6 inhibitor:

- Infections (particularly serious infections), including TB and opportunistic infections
  - Confirmed cases of active TB must also be recorded as an SAE.

- Malignancies
  - The Investigator will be asked to provide relevant medical information/documentation (e.g., pathology/histology reports) on all malignancy cases, whether considered serious or not, as these cases will be recorded in the safety database.
- Elevation of blood lipids (e.g., hypercholesterolemia, blood cholesterol increased, blood triglycerides increased, hypertriglyceridemia, and elevation of LDL)
- Systemic injection reactions and hypersensitivity reactions, including anaphylaxis
  - Refer to Appendix 6 (Section 13.6) for details on diagnosing anaphylaxis.
- GI perforation
- CV events
- Neutropenia, thrombocytopenia, leukocytopenia, and pancytopenia
- Hepatotoxicity
  - The Investigator will be asked to provide relevant medical information/documentation (e.g., laboratory test results, including tests for viral hepatitis and, if performed, liver biopsy) on all hepatotoxicity cases, whether considered serious or not, as these cases will be recorded in the safety database (see Section 7.6.3.4).
- Injection site reactions
- Demyelination in peripheral or central nervous system
- Autoimmune disorders.

All of the events listed above will be analyzed as AESIs; some of these events are further detailed below.

7.6.3.1 Infections

Frequency, duration, and severity of infectious complications along with those requiring treatment (e.g., antibiotic, antiviral, etc) will be monitored and evaluated. Investigators will also educate subjects, parents, and/or caregivers about the symptoms of infections and will provide instructions on dealing with these infections.

Physicians should exercise caution when considering the use of OKZ in subjects with a history of recurring infection or with underlying conditions (e.g., diabetes) that may

predispose subjects to infections. Study Treatment should not be administered to subjects with active or clinically significant infection. Vigilance for timely detection of serious infection is recommended for subjects receiving biologic agents for treatment of RA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reaction. Subjects must be instructed to contact their physician immediately when any symptom suggesting infection appears, in order to assure rapid evaluation and appropriate treatment. The Investigator may be asked to provide relevant medical information/documentation (e.g., result of bacterial examination or cultures).

Any infection that meets the criteria for seriousness should be reported as an SAE.

7.6.3.2 Systemic Injection Reactions, Including Anaphylaxis

A systemic injection reaction is any untoward medical hypersensitivity-like event, other than injection site reactions, occurring during or after study treatment administration that can be at least possibly attributed to the study treatment. Systemic injection reactions are further classified as acute and delayed based on timing and presentation of symptoms typical for hypersensitivity reactions.

Acute and delayed reactions to the study treatment should be reported according to the judgment of the Investigator, based on the typical clinical features.

Any systemic allergic reaction that meets the criteria for seriousness should be reported as an SAE.

Subjects will be observed for AEs at the study site during the 30 minutes following each administration of study treatment (or 2 hours after Visit 2), and subjects will be asked to contact the Investigator if any reactions occur within the 2 hours following study treatment injection.

Acute injection reactions are usually defined as at least 1 of the following signs or symptoms occurring during or within 2 hours of the study treatment injection:

- Hypotension
- Urticaria
- Flushing
- Facial or hand edema
- Throat tightness, oral cavity, or lip edema
- Headache

- Shortness of breath.

The Investigator should report any AE of acute systemic injection reaction as "anaphylaxis" if it meets the Clinical Criteria for Diagnosing Anaphylaxis, as specified in Appendix 6 (Section 13.6).

The study site must have adequate arrangements to manage anaphylactic reactions.

Delayed injection reactions are usually defined as at least 2 of the following 4 signs or symptoms occurring within 1 day to 14 days following the injection:

- Rash
- Fever (more than 100°F [38°C])
- Polyarthralgias
- Myalgias.

7.6.3.3 Gastroinestinal Perforation

Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticulitis and thus reduce the risk of GI perforations. Therefore, subjects should be made aware of the symptoms potentially indicative of diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise. Permanent discontinuation of study treatment is required for subjects who develop GI perforation.

Any GI perforation that meets the criteria for seriousness should be reported as an SAE.

7.6.3.4 Hepatotoxicity

The Investigator will be asked to provide relevant medical information/documentation (e.g., laboratory test results) for all serious and non-serious cases of potential hepatotoxicity.

Potential hepatotoxicity is defined as laboratory results that fulfill any of the following criteria (in all cases, AST may be substituted for ALT if ALT results are not available):

- ALT >3× to ≤5× ULN
- ALT >5× ULN
- ALT >3× ULN and total bilirubin >2× ULN

Laboratory results that satisfy any of the criteria for potential hepatotoxicity should be followed by a repeat test within 72 hours, which must include total bilirubin, direct and

indirect bilirubin, GGT, INR, alkaline phosphatase, creatine phosphokinase, and hematology assessment. After that, testing should be repeated at least weekly and followed until resolution, stabilization, or return to baseline values. Additional testing may be limited to ALT, AST, alkaline phosphatase, and bilirubin if all other laboratory results are within normal limits. The number of LFTs included in each repeat testing may be further reduced to include only those parameters which remain abnormal (i.e., abnormalities that stabilize, resolve, or return to within baseline values do not require repeat testing).

Potential hepatotoxicity events that fulfill any of the following criteria must also be recorded as SAEs in the eCRF (in all cases, AST may be substituted for ALT if ALT results are not available):

- ALT >3× ULN and total bilirubin >2× ULN
- ALT >8× ULN at any time, regardless of total bilirubin or accompanying symptoms
- ALT >5× ULN for ≥2 weeks, regardless of total bilirubin or accompanying symptoms
- ALT >3× ULN, accompanied by symptoms consistent with hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash)

For SAEs of potential hepatotoxicity, the Investigator should contact the Medical Monitor for guidance, as additional tests are needed to investigate all potential causes of liver toxicity (e.g., alcohol use, hepatitis infection, biliary tract disease, and concomitant medications). Work-up includes, but is not limited to:

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal/dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis (types A, B, C, D, and E), cytomegalovirus, Epstein-Barr virus, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin, biliary tract ultrasonography/imaging results, liver biopsy).
- Considering gastroenterology or hepatology consultations.

All additional investigations should be recorded in the eCRF via the EDC system, and all records should be kept as source documents at the study site.

7.6.3.5 Injection Site Reactions

An injection site reaction is any untoward medical event occurring at the injection site during or after study treatment administration that can be at least possibly attributed to the study treatment (i.e., the relationship cannot be ruled out).

An assessment of pain, redness, swelling, induration, hemorrhage, and itching at the injection site will be performed by a physician and recorded on the specific page of the eCRF. At all specified visits (see Table 1 or Table 2 [as applicable]), the assessment of injection site reactions will be made prior to any administration of study treatment. All local reactions observed will be monitored until they resolve.

7.6.4 Study Committees

An independent DSMB and CVAC will be established for this study.

Members of the DSMB and CVAC will consist of at least 3 independent experts appointed by R-Pharm based on their expertise. Committee members will not be Investigators in the study, nor will they have any conflict of interest with R-Pharm or its designee. Members of the DSMB and CVAC will only serve on their appointed committee.

Further details (e.g., frequency of data reviews and study committee composition and membership) will be provided in the predefined DSMB Charter and a separate CVAC Charter.

7.6.4.1 Data Safety Monitoring Board

The independent DSMB members will perform ongoing safety surveillance and provide recommendations to R-Pharm regarding study conduct. These recommendations will be based mainly on the review of AEs and laboratory parameters. In the event that the DSMB uncovers an issue that needs to be addressed by unblinding at the treatment group level, only members of the DSMB are permitted to conduct additional analysis of the unblinded safety data.

7.6.4.2 Cardiovascular Adjudication Committee

The CVAC will be responsible for evaluating MACE and will remain blinded to treatment assignment. The importance of the CVAC is to ensure that all potential MACE that have been reported are judged uniformly by a single group, using the same adjudication criteria.

Data on the following fatal and nonfatal potential MACE (as further defined in the CVAC Charter) will be collected and the events will be adjudicated by the CVAC (as well as assessed by the DSMB):

- Cardiovascular death
- Non-fatal myocardial infarction
- Non-fatal stroke of all classifications
- Transient ischemic attack
- Hospitalization for unstable angina requiring unplanned revascularization
- Non-fatal coronary revascularization procedures

7.6.5 Reporting of Adverse Events

Study site personnel will record any change in the condition(s), occurrence, and nature of any AEs, including clinically significant signs and symptoms of the disease under treatment in the study. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AEs eCRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”). All AEs related to protocol procedures must be reported to R-Pharm’s designee.

Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject’s medical record and on the AEs eCRF page.

All AEs that occur after the ICF is signed, regardless of severity, are to be recorded on the appropriate AE pages in the eCRF (either serious or nonserious). The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, and relationship to study treatment. Each event should be recorded separately.

Investigators will be instructed to report to R-Pharm’s designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study treatment, and/or drug delivery system via eCRF.

Study site personnel will record any dosage of study treatment that exceeds the assigned dosage in the protocol via eCRF.

Any clinically significant findings from laboratory test results, vital sign measurements, other procedures, etc. should be reported to R-Pharm’s designee via eCRF, EDC, and/or designated

data transmission methods. Investigators should use correct medical terminology/concepts when recording AEs on the AEs eCRF page, avoiding colloquialisms and abbreviations. Only 1 AE term should be recorded in the event field on the AEs eCRF page. For AEs other than injection-related reactions, a diagnosis (if known) should be recorded on the AEs eCRF page rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AEs eCRF page. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and potential relatedness to the investigational drug. The action taken and the outcome must also be recorded in the AE page of the eCRF.

7.6.5.1 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any subject responses suggestive of a possible AE are identified during study site review of the PRO questionnaires, study site staff will alert the Investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the subject's medical record per study site practice. If the event meets the criteria for an AE, it will be reported on the AEs eCRF.

7.6.5.2 Reporting of Serious Adverse Events

All SAEs that occur after the subject has signed the ICF, regardless of the Investigator's assessment on causality, must be recorded on the relevant pages of the eCRF and reported to R-Pharm according to protocol requirements.

Investigators must report the SAE within 24 hours of first becoming aware of the event. All SAEs must be reported via the EDC system by completing the relevant eCRF pages in English. In the event that the EDC system is not functioning, SAEs must be reported within 24 hours of first becoming aware of the event using the back-up paper SAE report form (instructions provided in the Investigator binders). Once the EDC system is operating normally again, Investigators must enter the SAE in the eCRF pages. All SAEs should be followed up until resolution or permanent outcome of the event or until the event is otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report. R-Pharm's designee is responsible for managing the safety database.

R-Pharm will be alerted of all SAEs occurring during a subject's follow-up regardless of the Investigator's assessment of causality. SAEs occurring after a subject has received the last dose of study treatment will be collected and reported to R-Pharm's designee through the end of the Follow-Up Period (i.e., for a period of 22 weeks after the last dose of study treatment), regardless of the Investigator's opinion of causality. The Investigator must also inform participating subjects of the need to inform the Investigator of any SAE that occurs within this period. Any SAE with a start date after the Follow-Up Period is not required to be reported unless the Investigator thinks that an event may be related to either the study treatment, study treatment administration, or a protocol procedure.

7.6.5.3 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

R-Pharm's designee will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, ethics committees, and Investigators, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to R-Pharm's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. R-Pharm's designee will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of OKZ or that would be sufficient to consider changes in the study treatment administration or in the overall conduct of the study. The study site will also forward a copy of all expedited reports to the relevant Independent Ethics Committee (IEC) or Institutional Review Board (IRB) in accordance with national regulations.

7.6.5.4 Follow-up of Adverse Events

Any AEs that occur after the subject has signed the ICF until the end of the Safety Follow-Up Period (i.e., 22 weeks after the last dose of study treatment) will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health, the Investigator does not expect any further improvement or worsening of the AE, or the subject is lost to follow-up. For AEs with a causal relationship to the study treatment, R-Pharm or its designee must concur with the Investigator's assessment.

For SAEs, nonserious AESIs, and pregnancies, R-Pharm's designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, or autopsy reports) in order to perform an independent medical assessment of the reported case.

7.6.5.5 Follow-up of Serious Adverse Events by Investigator

Any SAEs that occur after the subject has signed the ICF until the end of the Safety Follow-Up Period (i.e., 22 weeks after the last dose of study treatment), regardless of the Investigator's opinion of causality, will be followed-up. The Investigator should follow each SAE until the event has resolved to the baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. If the subject is lost to follow-up, the SAE will be categorized based on the Investigator's last assessment. Every effort should be made to follow all SAEs considered to be related to OKZ or study-related procedures until an outcome can be reported.

During the study, resolution of SAEs (with dates) should be documented on the SAE page of the eCRF and in the subject's medical record to facilitate source data verification. If, after follow-up, return to the baseline status or stabilization cannot be established, an explanation should be recorded on the SAE page of the eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome.

7.6.6 Clinical Laboratory Evaluations

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis (or signs or symptoms if a diagnosis is not possible) and is not a clinically significant worsening from the baseline laboratory parameter, it should be documented accordingly without being reported as a separate laboratory AE. The central laboratory will analyze the samples. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a Laboratory Manual. Additional and repeat laboratory testing not specified in Table 1 or Table 2 (as applicable) may be performed at the discretion of the Investigator either at the local laboratory or at the central laboratory to ensure that the safety of subjects is protected.

7.6.6.1 Laboratory Parameters

Unless otherwise noted, the central laboratory will be used in this study to analyze routine blood samples. Blood samples will be collected according to the study Schedule of Events in Table 1 or Table 2 (as applicable).

The following laboratory parameters will be evaluated:

- CRP: Since the results of this test may unblind study staff, results from the central laboratory will be provided for Screening and baseline only. The CRP results from

samples collected during the Treatment Period will only be revealed following database lock.

- ESR: Blood for ESR will be obtained at scheduled visits and tested locally. Since the results of this test may unblind study staff, testing will be performed, reviewed, and registered by unblinded study site staff who are not responsible for managing subjects. Test results will be provided to blinded study staff for baseline only. The ESR results from samples collected during the Treatment Period will only be revealed following database lock.
- Hematology: Red blood cell count, total and differential white blood cell count, hemoglobin, hematocrit, and platelet count
- INR, aPTT, and fibrinogen
- Chemistry Panel: Urea nitrogen, creatinine, fasting glucose, calcium, sodium, potassium, bicarbonate, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, and albumin
- Blood pregnancy test (at Screening for women of childbearing potential only)
- Urinary pregnancy testing (human chorionic gonadotropin) is required only for women who are of childbearing potential; may be repeated more frequently than indicated in Table 1 or Table 2 (as applicable) if required by local practices, IRB/IECs or local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected. Additional testing that is not specified in Table 1 or Table 2 (as applicable) should be reported in the eCRF as unplanned testing. Urinary pregnancy testing will be conducted locally using dipsticks provided by the central laboratory.
- Urinalysis: Specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase
- The infectious status of the following viruses will be assessed via measurement of the parameters in parentheses (at Screening only):
  - HIV (anti-HIV1 and anti-HIV2)
  - Hepatitis B (HBsAg, anti-HBs, and anti-HBc)
  - Hepatitis C (HCV Ab) Lipid panel: Total cholesterol, HDL, LDL, triglycerides, lipoprotein (a), apolipoproteins (apolipoprotein B [ApoB], apolipoprotein A1 [ApoA1], and ApoB:ApoA1 ratio), and adiponectin
- Cardiovascular risk panel: N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), and homocysteine

- HbA_{1c} (at Screening only)
- Anti-CCP and RF (at Screening and EoT Visit only)
- ANA and dsDNA antibodies
- IGRA (at Screening and Visit 14 only)
  - IGRA is to be performed at Screening (Visit 1) and the result is to be known prior to randomization to determine the subject's eligibility for the study (see exclusion criterion No. 19 in Section 5.3.2). If indeterminate, the IGRA can be repeated once during the Screening Period.
  - IGRA is to be performed at Visit 14 (Week 22) for all subjects who had a negative IGRA result at Screening. If indeterminate, the IGRA can be repeated once.
    - Subjects who had a positive IGRA result at Screening and were subsequently enrolled in the study following treatment for LTBI will not undergo the scheduled IGRA at Visit 14 (Week 22).
  - Details of the assessment are provided in the Laboratory Manual.
- ADAs: The actual sample collection date and exact time will be entered on the Immunogenicity Blood Collection eCRF page. Sampling problems will be noted in the Comments section of the eCRF. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. A Laboratory Manual will be provided to the Investigators with detailed information on sample collection, handling, and shipment. Tubes and preprinted labels will be provided by the central laboratory to the study sites.
- Pharmacogenetics and Biomarkers: The actual sample collection date and exact time will be entered on the corresponding Blood Collection eCRF pages. Sampling problems will be noted in the Comments section of the eCRF. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. A Laboratory Manual will be provided to the Investigators with detailed information on sample collection, handling and shipment. Tubes and preprinted labels will be provided by the central laboratory to the study sites.

Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the study site before study site initiation in a Laboratory Manual.

The laboratory sheets will be filed with the subject's source documents.

7.6.7 Vital Signs, Physical Findings and Other Safety Assessments

7.6.7.1 Physical Examination

A complete physical examination will be performed at Visit 1 (Screening), Visit 2 (Randomization), Visit 9 (Week 12), EoT or Visit 15 (Week 24), and Safety Follow-Up Visit SFU-3 (Week 44), as indicated in Table 1 or Table 2 (as applicable). A complete physical examination will include evaluation of general appearance, skin, head, eyes, ears, nose and throat, lymph nodes, respiratory, CV, GI including hepatobiliary assessment, musculoskeletal, endocrine system, neurological systems, and urogenital system.

At all other visits, a partial physical examination will be performed assessing the following: general appearance, skin (including site of study treatment injection), respiratory, CV, and GI.

All significant findings that are present at Screening must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after randomization that meet the definition of an AE must be recorded on the AEs eCRF.

7.6.7.2 Vital Signs

Vital signs (temperature, heart rate, BP, and respiratory rate) will be measured as indicated in Table 1 or Table 2 (as applicable), and when clinically indicated. Whenever possible, vital sign assessments should be performed by the same study site staff member and using the same validated device(s) throughout the study. Blood pressure and heart rate should be measured after the subject rests 5 minutes in a sitting position.

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Results in a change in RA treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

7.6.7.3 Body Weight and Height

Body weight (to the nearest 0.1 kilogram [kg]) and height (in cm) will be recorded at the time points specified in Table 1 or Table 2 (as applicable). Body weight and height should be

measured in indoor clothing without shoes. Whenever possible, body weight measurement should be performed by the same study site staff member and using the same validated scale throughout the study. The subject's body mass index will be calculated automatically in the eCRF.

7.6.7.4 Electrocardiogram

A standard 12-lead ECG will be performed at the time points specified in Table 1 or Table 2 (as applicable).

Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording.

The Investigator (if certified) or a certified designee will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. Clinically relevant abnormalities, including the baseline ECG, should be recorded on the AE eCRF page.

All ECG records collected during the study should have a printed copy kept as a source document at the study site (if the ECG record is printed on thermal paper, a photocopy should be made).

7.6.7.5 Evaluation of Chest X-ray

A chest X-ray (both lateral and posteroanterior) not older than 8 weeks evaluated and interpreted by a certified specialist at Screening as part of Screening procedures to confirm the absence of TB or other pulmonary infection will be acceptable; if no such chest X-ray is available, this should be performed. The Investigator should consult with a certified TB specialist or pulmonologist who is familiar with diagnosing and treating TB (as acceptable per local practice), if required. Films or images available at Screening and collected during the study should be evaluated by a certified specialist and kept as source documents.

7.6.8 Safety Monitoring

The R-Pharm's designee will monitor safety data throughout the course of the study. The designee will, as is appropriate, consult with the functionally independent subject safety therapeutic area physician, or clinical scientist, and review trends, laboratory data, and AEs at periodic intervals.

In the event that ongoing safety monitoring uncovers an issue that needs to be addressed by unblinding at the treatment group level, only members of the DSMB (an external advisory group for this study formed to protect the integrity of data) can conduct additional analyses of the safety data. See also Section 7.6.4 for details regarding the DSMB.

7.6.9 Tuberculosis Risk Questionnaires

The questionnaires "Tuberculosis Risk Questionnaire for Screening Visit" and "Tuberculosis Risk Questionnaire for Post-Screening Visits" (see Appendix 5 [Section 13.5]) should be used as source documents. The questionnaire "Tuberculosis Risk Questionnaire for Screening Visit" will be completed at Visit 1 (Screening), and the questionnaire "Tuberculosis Risk Questionnaire for Post-Screening Visits" will be completed at Visits 7, 10, 15, and SFU-2 as noted in Table 1 or Table 2 (as applicable).

At the Screening Visit, if question No. 1 (Does the subject have currently active TB disease or a history of active TB disease) or question No. 2 (Has the subject been in 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 the past 1.5 years) of the questionnaire "Tuberculosis Risk Questionnaire for Screening Visit" is answered "Yes" the subject is not allowed to enter the study (see exclusion criterion No. 19, Section 5.3.2). A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine the subject's risk of TB disease.

At all post-Screening visits, a "Yes" response on the "Tuberculosis Risk Questionnaire for Post-Screening Visits" should be treated as follows:

- Question 1: If a subject answers "Yes" study treatment should be discontinued if active TB is confirmed (see Section 6.11).
- Questions 2 through 6: if a subject answers "Yes" to any question, they should be assessed (TB risk questionnaire and physical examination) 12 weeks from the time of exposure to determine if the subject developed TB. The Investigator should consult with a certified TB specialist or pulmonologist, if needed.
- Questions 7 through 12: if a subject answers "Yes" to any question, this should trigger a careful assessment to determine if the subject developed TB (see Section 7.6.10).

This risk questionnaires are not to be used to exclude TB disease or confirm diagnosis.

7.6.10 Management of Tuberculosis

Subjects who develop evidence of latent or active TB once enrolled in the study (and receiving study treatment) must immediately discontinue further administration of study treatment, and the subject should be examined by a certified TB specialist or pulmonologist who is familiar with diagnosing and treating TB (as acceptable per local practice).

If active TB is confirmed, the subject must permanently discontinue study treatment (see Section 6.11). Confirmed active TB is an SAE that must be recorded on the relevant pages of the eCRF and provided to the Sponsor in accordance with SAE reporting requirements. Details regarding follow-up of SAEs are provided in Section 7.6.5.5.

If latent TB is confirmed, the subject may resume the administration of study treatment if active TB is ruled out by a certified TB specialist or pulmonologist who is familiar with diagnosing and treating TB (as acceptable per local practice), the subject starts prophylactic treatment of LTBI according to country-specific/CDC guidelines (see Appendix 7 [Section 13.7]), and the subject agrees to complete the entire course of recommended therapy. Study treatment should not be administered until active TB is ruled out and the subject starts prophylactic LTBI therapy. Confirmed latent TB should be recorded as an AESI on the relevant pages of the eCRF. Details regarding follow-up of AEs are provided in Section 7.6.5.4.

7.7 Appropriateness of Measurements

All assessments made in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

8. QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (GCP) (CPMP/International Council for Harmonisation [ICH]/135/95), R-Pharm and R-Pharm's designee are responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meetings.
- Central laboratories for clinical laboratory parameters.
- Site initiation visit.
- Early site visits after enrollment.
- Routine study site monitoring.
- Ongoing study site communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, R-Pharms (or its designee's) Clinical Quality Assurance Department may conduct periodic audits of the study processes, including study site, site visits, central laboratories, vendors, clinical database, and final clinical study report. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to R-Pharm's designee and regulatory authorities.

8.1 Monitoring

R-Pharm's designees will perform all monitoring functions within this clinical study. The designee's monitors will work in accordance with established SOPs and have the same rights and responsibilities as monitors from R-Pharm. Monitors will establish and maintain regular

contact between the Investigator and R-Pharm. There will be both blinded and unblinded monitors, as appropriate.

Monitors will evaluate the competence of each study site, informing R-Pharm about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each study site while subjects are enrolled in the study. The monitor will make written reports to R-Pharm on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). Please refer to the Monitoring Plan for further details.

Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments of R-Pharm's designee.

An EDC system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized study site staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study site staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study treatment, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events and medical history will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

8.2 Quality Assurance Audit

Study sites, the study database, and study documentation may be subject to Quality Assurance audit during the course of the study by R-Pharm or R-Pharm's designee on behalf of R-Pharm. In addition, inspections may be conducted by regulatory bodies at their discretion.

9. STATISTICS

9.1 Determination of Sample Size

Given that the study would be considered successful if at least 1 of the 2 OKZ dose regimens is shown to be efficacious and that a priori both OKZ dose regimens are assumed to be efficacious, we are using disjunctive power (i.e., a probability of detecting a significant treatment effect for at least 1 OKZ treatment regimen), as a criterion for the estimation of the sample size. Sample size requirements are calculated to provide sufficient disjunctive power to evaluate the primary endpoint (ACR20 response rate at Week 12) and the first secondary endpoint (DAS28 [CRP] <3.2 at Week 12). Sample size was estimated taking into account a multiplicity control procedure and the resulting α adjustment that will be used in this study to control an overall Type I error rate in the strong sense at a 1-sided $\alpha = 0.025$ across the primary and secondary endpoints. More specifically, the α-control strategy will be based on using the Bonferroni adjustment for the tests related to each of the 2 OKZ dose regimens versus placebo (i.e., using the 1-sided $\alpha = 0.0125$ for each dose). A gate-keeping strategy will be used for tests associated with the primary and secondary endpoints for each OKZ dose regimen independently, with a fixed order of hypothesis tests for the primary and secondary endpoints within each OKZ dose regimen. Sample size was estimated based on simulation that implemented the above α adjustment and gate-keeping procedure including the primary endpoint of ACR20 response rate at Week 12 and the first secondary endpoint. Based on this simulation, an adequate sample size was selected to provide sufficient disjunctive power for the primary endpoint and the first secondary endpoint based on DAS28 (CRP) <3.2 rate at Week 12. For the first secondary endpoint, the disjunctive power represents a probability of establishing a significant treatment effect for 1 or 2 OKZ dose regimens for the primary endpoint and a significant treatment effect for 1 or 2 OKZ dose regimens for the first secondary endpoint, conditional on the fact that each dose regimen tested for the secondary endpoint must have null hypothesis previously rejected for the primary endpoint based on a fixed order of testing as per the gate-keeping procedure.

Treatment effect assumptions used in the simulation-based sample size calculations, involving the primary and the first secondary endpoint are as follows.

The ACR20 response rate at Week 12 for the placebo group is estimated to be 25% in this study population (Genovese et al, 2008; Keystone et al, 2004; Weinblatt et al, 2003). The OKZ ACR20 response rates for 64 mg q4w and q2w treatment groups at Week 12 are expected to be at least 50% and 55% respectively, resulting in an expected difference in ACR20 response rates of 25 and 30 percentage points between respective OKZ treatment groups and placebo.

The DAS28 low disease activity (based on DAS28 [CRP] <3.2) response rate at Week 12 is estimated to be 10% in the placebo group (van der Heijde et al, 2006) and 22% and 30% in 64 mg q4w and q2w OKZ treatment groups respectively, resulting in an expected difference of 12 and 20 percentage points between respective OKZ treatment groups and placebo.

The references cited above for ACR20 and DAS28 response rates are assumed to reflect approximately 10% of subjects discontinuing randomized treatment prior to Week 12. In this study, subjects who discontinue prior to Week 12 will be classified as nonresponders for the primary endpoint of ACR20 at Week 12 as well as for the secondary endpoint of DAS28 (CRP) <3.2 at Week 12.

The primary endpoint as well as the secondary endpoints that are binary in nature will be analyzed using a 2×2 chi-squared test for equality of proportions for each OKZ treatment group compared with placebo.

Based on the treatment effect assumptions and the methodology for estimating sample size via simulation to ensure sufficient disjunctive power as described above, a sample size of 420 subjects randomized in a 1:1:1 ratio (140 subjects per treatment group) will yield 100% disjunctive power for testing the primary hypothesis (ACR20 at Week 12) and 98% disjunctive power for the evaluation of the secondary endpoint of DAS28 (CRP) <3.2 rate at Week 12.

9.2 Data to be Analyzed

Data handling will be the responsibility of R-Pharm's designee. The data will be inspected for inconsistencies by performing validation checks.

9.3 Analysis Populations

- Intent-to-treat (ITT) population: The ITT population will include all randomized subjects. Subjects will be analyzed according to the treatment group to which they were randomized. The ITT population will be the primary analysis population.
- Modified Intent-to-treat (mITT) population: The mITT population will include all randomized subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to the treatment group to which they were randomized. The mITT population, if sufficiently different from the ITT population (>5% of ITT subjects excluded from the mITT population across all treatment groups), will be used for supportive analyses of the primary and secondary efficacy endpoints.
- Per Protocol (PP) population: The PP population will include all ITT subjects who do not have any major protocol violations. Subjects will be analyzed according to the

treatment group to which they were randomized. Major protocol violations will be defined and the inclusion of subjects in the PP population will be finalized prior to study unblinding. The PP population will be used for supportive analyses of the primary and secondary efficacy endpoints.

- Safety population: The safety population will include all subjects who receive at least 1 dose of study treatment. Subjects in the safety population will be analyzed according to the treatment they actually received. In addition to the primary safety analysis, the incidence of AEs will be analyzed separately for subjects administered an additional DMARD as rescue medication during the Treatment Period and for subjects who did not receive rescue medication.
- Pharmacokinetic population: The PK population will include all subjects who receive at least 1 dose of OKZ and have sufficient plasma samples for PK assessments without important protocol deviations or events affecting the PK results. All subjects in the PK population must have at least 1 evaluable postdose OKZ concentration. To be included in the PK subpopulation, subjects must have received at least 1 dose of OKZ, received OKZ on Week 0, and have sufficient plasma samples to allow calculation of at least 1 PK parameter.

9.4 Statistical Methods

All data collected in the clinical database will be presented in subject data listings.

Unless otherwise specified, baseline value for each parameter will be defined as the last available assessment prior to the first dose of the study treatment.

No adjustment for covariates will be included in the primary analysis of the primary endpoint or the analysis of the secondary and other endpoints that are binary in nature. Analyses of the continuous efficacy endpoints will be adjusted for baseline values of the corresponding parameters.

Data collected after the initiation of rescue medication (as described in Section 6.13.3) will be used in all main analyses.

The primary endpoint as well as secondary and other endpoints that are binary in nature will be analyzed using a 2×2 chi-squared test for equality of proportions for each OKZ treatment group compared with placebo.

Endpoints that are continuous in nature will be analyzed using an analysis of covariance (ANCOVA) model adjusted for the baseline value of the corresponding parameter.

Continuous efficacy endpoints will be summarized using descriptive statistics such number of available values (n), mean, median, minimum, maximum, and standard deviation for the 3 treatment groups, respectively. Categorical efficacy endpoints will be summarized by the number and percentage of subjects in each category.

Efficacy analyses will be conducted using the ITT population. Supportive analyses of the primary and secondary efficacy endpoints will be conducted using the mITT (if sufficiently different from the ITT population) and PP populations. All comparisons for efficacy assessments will be carried out based on treatment groups to which the subjects were originally randomized.

Safety analyses will be done according to the treatment subjects actually received.

Details for the statistical analysis will be specified in the Statistical Analysis Plan (SAP) to be written and finalized prior to the unblinding of the database. The statistical analysis will be performed by R-Pharm's designee.

All statistical analyses will be conducted using SAS® version 9.2 or higher for Windows.

9.4.1 Disposition of Study Subjects

Disposition of study subjects will be summarized by treatment group as the number and percentage of subjects screened (signed ICF), randomized, included in each analysis population as defined in Section 9.3, completing the study treatment, discontinuing from the study treatment overall and by reason for discontinuation, completing the study, discontinuing from the study overall and by reason for discontinuation, and enrolling into the OLE study. The number and percentage of subjects discontinuing study treatment by visit in each treatment group will also be summarized. A Kaplan-Meier plot of time to treatment discontinuation in each treatment group will be presented.

Determination of major protocol deviations and inclusion of subjects in the analysis populations will be finalized and approved by R-Pharm prior to the study unblinding.

9.4.2 Demography and Baseline Characteristics

Demographic information, baseline characteristics, and prior and concomitant medications will be presented using descriptive statistics or frequency counts, as appropriate, for continuous and categorical variables.

9.4.3 Medical History

A complete medical history will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, CV, GI/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric,

endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse, or any other diseases or disorders. Medical history terms will coded using the most recent version of the MedDRA, listed by subject, and summarized by SOC and PT in each treatment group.

9.4.4 Prior and Concomitant Medications

Prior and concomitant medications will be separately summarized as the number and percentage of subjects by World Health Organization (WHO) drug class, preferred name, and treatment. Medications will be coded using the WHO Drug dictionary, Anatomic Therapeutic Class (ATC) level 2, and preferred drug name.

Prior medications will be distinguished from concomitant medications by a stop date before the first dose of the study treatment. Medications that stopped on the same date as the first dose of the study treatment will be considered a prior medication. Any medication that a subject started before the first dose of double-blind study treatment and continued to take during the study, and any medication that the subject began taking after the first dose of study treatment will be classified as concomitant.

Medications administered as rescue medication (as described in Section 6.13.3) will also be summarized as the number and percentage of subjects by WHO drug class, preferred name, and treatment.

9.4.5 Exposure and Compliance

Exposure to study treatment and compliance will be summarized descriptively by treatment group for the Safety population.

Exposure to double-blind study treatment will be calculated as the number of doses received in the course of the study. Duration of exposure will be defined as the total number of days a subject was exposed to study treatment, calculated as:

Date of last dose – Date of first dose + 1 day.

Overall compliance (expressed as a percentage) will be calculated as:

(Exposure to double-blind study treatment / Number of doses subject was expected to receive) × 100.

Duration of exposure and compliance will be calculated based on all planned doses (placebo and active treatment), as appropriate for each treatment group. For the OKZ 64 mg q4w dosing regimen, both OKZ and placebo doses will be used in the calculations.

9.4.6 Multiple Hypothesis Testing

Each of the OKZ treatment groups (64 mg q2w and q4w) will be compared with placebo for each of the primary, secondary, and other endpoints. The overall Type I error rate will be controlled for testing hypotheses of the primary and secondary endpoints at the overall 1-sided $\alpha = 0.025$. The α-control strategy will be based on using the Bonferroni adjustment for the tests related to each of the 2 OKZ dose regimens versus placebo (i.e., using the 1-sided $\alpha = 0.0125$ for each dose). A gate-keeping strategy will be used for tests associated with the primary and secondary endpoints for each OKZ dose regimen independently with the same order of testing as the secondary endpoints are defined above. In other words, each OKZ dose regimen will be tested at 1-sided $\alpha = 0.0125$ for a given endpoint if null hypotheses are rejected at 1-sided $\alpha = 0.0125$ for this dosing regimen for all previous endpoints based on the established order. Conversely, the testing will stop for a given OKZ dose regimen at the endpoint for which the null hypothesis is accepted at 1-sided $\alpha = 0.0125$.

The above multiplicity control procedure will be applied to the primary analysis of the primary and secondary efficacy endpoints based on the ITT population, and will not be applied to sensitivity analyses of these endpoints.

9.4.7 Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects achieving an ACR20 response and remaining on randomized treatment and in the study at Week 12, analyzed using the ITT population as the primary efficacy analysis. Supportive analyses of the primary endpoint will also be done using the mITT, if sufficiently different from the ITT population, and PP populations.

The ACR20 response at Week 12 for each of the OKZ 64 mg treatment groups (q2w and q4w) will be compared with placebo using a 2×2 chi-squared test for equality of proportions.

The overall Type I error rate will be controlled using a procedure in the strong sense at a 1-sided $\alpha = 0.025$ for testing multiple hypotheses for the 2 OKZ treatment groups versus placebo across the primary and secondary endpoints as described in Section 9.4.6.

As a supportive analysis, the difference between proportions of responders in each of the OKZ treatment groups and placebo (relative risk) will be estimated together with the corresponding 97.5% 2-sided confidence interval for difference of proportions using the Newcombe hybrid score method.

Missing data and data collected post premature study treatment discontinuation will be handled as described in Section 9.4.9.1.

9.4.8 Analysis of Secondary and Other Efficacy Endpoints

Analysis of secondary and other efficacy endpoints defined in Sections 4.2 and 4.3 will be based on the ITT population. Supportive analyses of the secondary endpoints will also be done using the mITT, if sufficiently different from the ITT population, and the PP population.

Secondary and other efficacy endpoints that are binary in nature will be analyzed using the same methodology as the primary endpoint.

Secondary and other efficacy endpoints that are continuous in nature will be analyzed using an ANCOVA model adjusted for the baseline value of the corresponding parameter.

Multiplicity control procedure to be applied for hypothesis testing related to the secondary endpoints is described in Section 9.4.6.

Missing data and data collected post premature study treatment discontinuation will be handled as described in Section 9.4.9.1.

9.4.9 Handling of Missing Data and Data Following Premature Discontinuation of Randomized Treatment

9.4.9.1 Primary Analysis of Primary, Secondary, and Other Efficacy Endpoints

Data Following Premature Discontinuation of Randomized Treatment

In this study, subjects who discontinue randomized treatment prematurely will be required to remain on study and be evaluated as per the planned Schedule of Events. For the main analysis of all binary endpoints, inability to remain on randomized treatment through the time point of interest is defined as treatment failure (non-response). For the main analysis of continuous endpoints, subjects who discontinue randomized treatment prematurely but remain on study through the time point of interest will be included using all collected measurements, including those from assessments post treatment discontinuation.

Missing Data Resulting from Study Withdrawal

The main method for handling missing data resulting from premature withdrawal of a subject from the study will be based on a clinical approach where no treatment benefit will be attributed to study treatment at any time point post-study withdrawal, if the subject was unable to complete the study for the planned duration.

Therefore, for all binary endpoints, all subjects who discontinue prematurely, regardless of reason, will be considered as nonresponders with respect to the definition of the corresponding endpoint.

Similarly, for all endpoints that are continuous in nature, a return to baseline values will be assumed and will be implemented using a multiple imputation (MI) methodology allowing to account for the uncertainly of missing data according to the methodology of Rubin (Rubin, 1987). Imputed values will be sampled from a posterior Bayesian distribution of the baseline values of each continuous parameter (for all treatment groups combined) using a regression imputation model with age, sex, time from RA diagnosis to first study dose, and duration of prior MTX treatment as predictor variables. Multiply imputed data will be analyzed with an ANCOVA model and the results will be combined using the Rubin's rule (Rubin, 1987). Additional details will be provided in the SAP.

Intermediate Missing Data

Missing data may also result from missed intermediate visits for subjects who completed the study. For all binary endpoints, missing intermediate responder status will be imputed from the surrounding visits. If the status at visits both before and after the missed visit is classified as responder, the subject will be considered a responder at the missed visit. Otherwise, the subject will be considered a nonresponder. If an assessment for a given binary endpoint at the last visit is missing for a completing subject, data from the 2 previous visits will be used with the same logic for determining the response status. For the ACR20/50/70 endpoints, if only some components of the response criteria are missing but the available components allow classifying the subject as a responder, the responder category will be used. Otherwise, the method based on surrounding visits as described above will be applied. Similarly, for all continuous endpoints, an average of values from the surrounding visits will be imputed for the missing visit.

9.4.9.2 Sensitivity Analyses of Efficacy Endpoints

All sensitivity analyses will be performed based on the ITT population. Multiplicity adjustment procedure will not be applied for the sensitivity analyses. Other sensitivity analyses in addition to those described below may be performed and will be specified in the SAP.

Sensitivity to Data Following Premature Discontinuation of Randomized Treatment

Supportive analyses will be performed to assess the effect of standard of care treatment that the subjects may receive after premature discontinuation of randomized treatment while the subjects remain on study and continue to be evaluated.

In this supportive analysis, all binary efficacy endpoints will be defined regardless of adherence to randomized treatment through the time point of interest. Definitions will be based on the criteria of achieving the corresponding clinical response (e.g., ACR20) using all data collected at the time point of interest, i.e., including data collected post premature

discontinuation of randomized treatment. Subjects who discontinue from study overall, will be considered nonresponders at time points after study discontinuation.

For the supportive analysis of continuous endpoints, data collected post premature discontinuation of randomized treatment will be excluded and replaced with values imputed based on the return to baseline approach implemented with MI as described in Section 9.4.9.1.

These supportive analyses will be performed for all efficacy endpoints.

Sensitivity to Missing Data Assumptions

The method of handling missing data that considers discontinued subjects as nonresponders or imputes continuous data with baseline values may be regarded as not conservative if the proportion of subjects dropping out is greater in the placebo group than in the OKZ treatment groups. To address a possibility of this scenario, analysis of primary and secondary efficacy endpoints will be repeated using all collected data (including data post premature study treatment discontinuation) but with missing data after study withdrawal imputed under the following assumptions. Missing post-study withdrawal data for subjects discontinuing from the placebo group will be imputed under the assumption of the Missing-at-Random (MAR) mechanism, where these discontinued subjects are assumed to have post withdrawal values in line with similar placebo subjects who remained in the study, taking into account their values observed prior to discontinuation. For subjects discontinuing from the OKZ treatment groups, missing post withdrawal data will be imputed from the same MAR-based imputation model estimated from the placebo subjects, assuming that after discontinuation, the OKZ subjects will drift towards the mean response of the placebo group. This approach is likely to result in more favorable imputations for the placebo group compared with the nonresponder/return to baseline assumption, while for the OKZ treatment groups, it will not assume a treatment effect beyond the study effect and the effect of the background MTX therapy. This approach will be more conservative compared to the primary analysis if the proportion of subjects discontinuing from the study is greater in the placebo group than in the OKZ treatment groups.

This approach will be implemented with MI using 2 steps. First, intermediate missing data of each continuous parameter will be multiply imputed under the MAR assumption within each treatment group using a multivariate normal imputation model and the Markov chain Monte Carlo (MCMC) method. Second, intermediate missing data imputed in this way will then be used together with observed data for the estimation of the MAR-based model from the placebo group, which will be done using sequential regression imputation models applied to each continuous parameter (Ratitch et al, 2013). The MAR-based placebo imputation model for each parameter will be estimated based on data from placebo subjects and will

include baseline value of the corresponding parameter and all post-baseline values prior to study discontinuation as explanatory variables. Post study discontinuation missing values in all 3 treatment groups will then be imputed from this single placebo imputation model.

Binary endpoints will then be computed from the multiply imputed data regardless of adherence to randomized treatment through the time point of interest based on the criteria of achieving the corresponding clinical response. Multiply imputed datasets will be analyzed using the same methods as in the primary analysis, followed by combining the results using Rubin's rule (Rubin, 1987).

Additionally, for the primary and secondary endpoints that are binary in nature, a tipping point analysis will be performed. First, binary response status at the time point of interest will be computed using all collected data regardless of adherence to randomized treatment through the time point of interest based on the criteria of achieving the corresponding clinical response. For subjects who withdraw from the study overall, all possible combinations of the number of responders and nonresponders in each treatment group will be considered. The results of analysis for all possible combinations will be summarized graphically, depicting a boundary between combinations that result in a statistically significant treatment effect vs not statistically significant. Clinical plausibility of the combinations on the boundary will be discussed in the Clinical Study Report to evaluate robustness of study conclusions to missing data.

For the secondary endpoint that measures physical ability based on the HAQ-DI improvement at Week 12, a continuous responder analysis will also be performed. Subjects will be considered responders at a specified improvement threshold if they experience percent improvement in the HAQ-DI score from baseline to Week 12 that is greater or equal to the specified threshold and if they remain on the randomized treatment and in the study through Week 12. This analysis will be performed for a range of improvement thresholds from 0 to 100% in 5% increments. The results will summarized using a graph of proportion of responders in each treatment group versus improvement thresholds.

Sensitivity to Data Following Initiation of Rescue Medication

Sensitivity analyses classifying subjects who receive any rescue medication as nonresponders will be performed for binary efficacy endpoints defined at time points from Week 16 to Week 24.

9.4.10 Pharmacokinetic Analyses

Pharmacokinetic concentrations for OKZ in plasma will be summarized descriptively by scheduled collection time and dose regimen. Time to steady state will be graphically evaluated for the OKZ trough data collected over the study period.

For the PK subpopulation, plasma OKZ PK parameters will be summarized descriptively by dose regimen and study day. Accumulation of OKZ over time will be evaluated descriptively, and if appropriate with an exploratory inferential analysis. Pharmacokinetic relationships will be explored graphically and with linear or nonlinear modeling approaches, as appropriate. Data collected in this study may be combined with data from other OKZ studies in support of population PK analyses.

Concentration data for the ADA/PK matched subjects will only be analyzed and presented as part of the PK summaries if the subject has a positive ADA response during the Treatment Period. These data will be included the population PK analyses, as appropriate.

The related endpoints are described in in Section 4.4. Further details for the PK analysis will be provided in the SAP.

9.4.11 Pharmacokinetic/Pharmacodynamic Correlations

The PK/PD relationship and immunogenicity of OKZ will be determined as described in the endpoints by Section 4.5. Analyses may include statistical comparisons and/or population PK/PD analyses. Further details for evaluation of PK/PD and PK/safety correlations will be provided in the SAP or a separate population PK/PD analysis plan.

9.4.12 Immunogenicity

Immunogenicity results including overall ADA results (Screening, confirmatory, and titers, as appropriate), neutralizing ADA results, and the time course of antibodies (defined as the time to first observation of a positive ADA response) will be listed. The number and percentage of subjects testing positive for ADAs or neutralizing antibodies will be summarized by dose treatment group over time. If applicable, the time course of antibodies may be summarized by treatment group using appropriate descriptive statistics.

9.4.13 Pharmacogenetics

The exploratory PG studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

9.4.14 Biomarkers

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of drug action or disease, and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g., principal component analysis) between subject groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study and thus the analysis of this data will be data driven.

9.4.15 Safety Analyses

Analysis of safety endpoints (see Section 4.7) will be done based on the safety population. Subjects in the safety population will be analyzed according to the treatment they actually received. Additionally to the primary safety analysis, the incidence of AEs will be analyzed separately for subjects administered additional DMARDs as rescue medication during the period of treatment without rescue medication and with rescue medication.

Major components for the safety analysis will include:

- AEs will be solicited at every study visit, recorded, and coded according to the most recent version of the MedDRA.
- SAEs.
- Vital signs and physical examination findings.
- Laboratory parameters.
- ECG and other specialized tests findings.

All safety assessments will be summarized in a descriptive manner. Further details will be provided in the SAP.

9.4.15.1 Adverse Events

All AEs will be analyzed in terms of descriptive statistics and qualitative analysis. Adverse events will be listed for each subject and summarized by SOC and PT according to the most recent version of the MedDRA. In addition, summaries of AEs by severity (evaluated using the CTCAE version 4.0) and relationship to study treatment will be presented. All safety and tolerability data recorded during the study will be listed and summarized by treatment group, and over time, as appropriate. Additionally to primary safety analysis, the incidence of AEs

will be analyzed separately for subjects administered additional DMARD as rescue medication during the period of treatment without rescue medication and with rescue medication.

Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity after the first administration of the study treatment. Adverse event summaries will include incidence of TEAEs, SAEs including deaths, AEs that led to study treatment discontinuation, and AEs by maximum severity and relationship to study treatment. All summaries will be presented by MedDRA SOC and PT for each treatment group.

Safety/tolerability and AE data will be presented in individual listings.

9.5 Subgroup Analysis

All subgroup analyses will be exploratory (post hoc) in nature. The details of these analyses will be described in the SAP and provided prior to the database lock. No specific subgroup analysis will be described in details in the protocol.

9.6 Safety Monitoring Committees

A DSMB and CVAC will oversee the study from a safety and CV monitoring perspective, as described in Section 7.6.4.

9.7 Interim Analyses

No interim analyses are planned for the study.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee

An IRB/IEC should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will provide R-Pharm or R-Pharm's designee with documentation of IRB/IEC approval of the protocol and the ICFs before the study may begin at the study site(s). The Investigator should submit the written approval to R-Pharm or its designee before enrolment of any subject into the study.

R-Pharm or its designee should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to R-Pharm or R-Pharm's designee of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

R-Pharm or its designee will handle the distribution of any of these documents to the national regulatory authorities.

R-Pharm or its designee will provide Regulatory Authorities, IRBs/IECs, and Investigators with safety updates/reports according to local requirements, including SUSARs, where relevant.

Each Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study treatment. R-Pharm or its designee will provide this information to the Investigator so that he/she can meet these reporting requirements.

10.2 Ethical Conduct of the Study

The GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to

assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

10.3 Subject Information and Informed Consent

The ICFs (i.e., for the main study subjects, PK subpopulation, and for PG) will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF(s) contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

All ICFs must be available in the local and vernacular languages required at the study site and include subject information sheets/brochures that outline the study procedures. All ICF(s) must be signed and dated by the subject or a legally acceptable representative.

For subjects who are unable to read and write, the subject information sheet and ICF(s) should be read to the subject in his/her native language in the presence of an impartial witness who is literate and not affiliated with the study. The subject having understood the information given to him/her in the presence of an impartial witness will thumbprint the ICF(s) and the same will be countersigned by the impartial witness. If the subject or legally acceptable representative cannot read, then an impartial witness will witness and attest the entire consent process and will be required to sign the consent form. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including Screening tests and assessments.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatment. The Investigator will provide each subject with a copy of the signed and dated consent form while the originals will be retained in the Investigator's records.

10.4 Subject Data Protection

The ICF(s) will incorporate or, in some cases, be accompanied by a separate document incorporating wording that complies with relevant data protection and privacy legislation. R-Pharm or R-Pharm's designee will not provide individual results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Information about study subjects will be kept confidential and managed according to the regulatory requirements.

11. STUDY ADMINISTRATION

11.1 Administrative Structure

A list of the key individuals from R-Pharm and R-Pharm's designee who will contribute to this study and their roles will be available in the Study Reference Manual, kept on file, and updated as required.

The telephone and fax number of the study medical contact are listed in the Investigator Folder provided to each study site.

The 24-hour emergency medical contact number for this study is +1 973-659-6677 (alternate number: +1 570-819-8565)

11.2 Study and Study Site Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or study site staff, as appropriate, including the following:

- Return of all study data to R-Pharm.
- Resolution of data queries.
- Accountability, reconciliation, and arrangements for unused study treatment.
- Review of study site, study records for completeness.
- Review requirements for record retention and audit responsibilities.

11.3 Study Discontinuation

The study may be discontinued at any time by the IRB/IEC, R-Pharm, or regulatory agencies as part of their duties to ensure that research subjects are protected.

R-Pharm reserves the right to temporarily suspend or prematurely discontinue this study either at a single study site or at all study sites at any time for reasons including safety or ethical issues or severe non-compliance. If R-Pharm determines such action is needed, R-Pharm will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, R-Pharm will provide advance notification to the Investigator of the impending action prior to its taking effect.

R-Pharm will promptly inform all other Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If

required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to R-Pharm or its designee. In addition, arrangements will be made for return of all unused study treatment in accordance with R-Pharm's applicable procedures for the study.

Financial compensation to Investigators and/or institutions will be in accordance with the agreement established between the Investigator and R-Pharm.

11.4 Data Handling and Record Keeping

Information about study subjects will be kept confidential and managed according to the regulatory requirements. It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted.

Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to R-Pharm, who agrees to abide by the retention policies. Written notification of transfer must be submitted to R-Pharm. The Investigator must contact R-Pharm prior to disposing of any study records.

No records should be disposed of without the written approval of R-Pharm.

11.5 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the complete reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these source documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject's evaluation checklists, pharmacy dispensing records, recorded data

from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, radiographs, subject's records, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

The Investigator will allow the authorized R-Pharm's designee and authorized regulatory authorities and IRBs/IECs to have direct access to all documents pertaining to the study, including individual Subject medical records, as appropriate.

11.6 Investigator Information

11.6.1 Investigator Obligations

The Investigator is responsible for ensuring that all study site staff, including sub-Investigators, adhere to all applicable regulations and guidelines, including local laws and regulations, regarding clinical studies both during and after study completion.

The Investigator is responsible for informing the IRB/IEC of the progress of the study, for obtaining annual IRB/IEC renewal, and informing the IRB/IEC of completion of the study, and will provide the IRB/IEC with a summary of the results of the study.

The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements of European Commission Directive (2001/20/EC Apr 2001) and/or European Commission Directive (2005/28/EC Apr 2005) and/or US Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56, and 312, and/or other applicable local or regional regulations.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IRB/IEC in compliance with local regulatory requirements. The Investigator and R-Pharm will sign the protocol to confirm this agreement.

11.6.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to R-Pharm or its designee. By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

11.6.3 Publication Policy

R-Pharm shall retain the title and the right to publish all documentation, records, raw data, specimens or other work product generated pertaining to the study ("data") conducted by the study site (site includes the Investigator and the institution) as defined in the applicable protocol or study plan or study agreement. The study site shall maintain confidentiality and not disclose or divulge such "Data" to any third party. However, the study site may seek permission to publish such "Data" for limited purpose and such "Data" may be published by the study site only upon receipt of prior written approval from R-Pharm.

11.7 Financing and Insurance

R-Pharm is the Sponsor of the study. R-Pharm will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of the insurance will be kept in the study files.

R-Pharm has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

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13. APPENDICES

13.1 Appendix 1: Steinbrocker Functional Classification

Table 1. Classification of functional capacity in rheumatoid arthritis*

Class I	Complete functional capacity with ability to carry on all usual duties without handicaps
Class II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
Class III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care
Class IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care

* Steinbrocker criteria; reprinted, with permission, from *Journal of the American Medical Association* (1).

13.2 Appendix 2: New York Heart Association Functional Capacity Classifications

- Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
- Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

13.3 Appendix 3: American College of Rheumatology 2010 Criteria

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvement	
1 large joint	0
2−10 large joints	1
1−3 small joints (with or without involvement of large joints)	2
4−10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 Weeks	0
≥6 Weeks	1

Abbreviations: anti-CCP = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor.

13.4 Appendix 4: Methotrexate Dose Reduction Guidelines

ALT and/or AST	Total Bilirubin	Repeat Laboratory	MTX	Study Treatment
1× to ≤2× ULN	<2× ULN	No need	No change	No change
>2× to ≤3× ULN	<2× ULN	Within 1 week	No change or can consider reduction in dose	No change
If repeat >2× to ≤3× ULN	<2× ULN	Within 1 week	Reduce dosage and follow LFTs	No change
>3× to ≤8× ULN (without the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash)	≤2× ULN	Within 72 hours of initial finding, and then at least weekly after last finding until resolution, stabilization, or return to baseline values	Hold MTX until LFTs normalize or return to baseline and consider restarting at lower dose	No change
If repeat >3× to ≤8× ULN (without the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash)	≤2× ULN	Within 72 hours of initial finding, and then at least weekly after last finding until resolution, stabilization, or return to baseline values	Hold MTX until LFTs normalize or return to baseline and consider restarting at lower dose	Hold and consider restarting after discussion with the R-Pharm Medical Advisor or designee
>3× ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	≤2× ULN	Within 72 hours of initial finding, and then at least weekly after last finding until resolution, stabilization, or return to baseline values	Hold MTX. Follow local Standard of Care.	Permanently discontinue study treatment
>3× ULN	>2× ULN	Within 72 hours of initial finding, and then at least weekly after last finding until resolution, stabilization, or return to baseline values	Hold MTX. Follow local Standard of Care.	Permanently discontinue study treatment
>5× ULN for more than 2 weeks	≤2× ULN	Within 72 hours of initial finding, and then at least weekly after last finding until resolution, stabilization, or return to baseline values	Hold MTX. Follow local Standard of Care.	Permanently discontinue study treatment

ALT and/or AST	Total Bilirubin	Repeat Laboratory	MTX	Study Treatment
>8× ULN	≤2× ULN	Within 72 hours of initial finding, and then at least weekly after last finding until resolution, stabilization, or return to baseline values	Hold MTX. Follow local Standard of Care.	Permanently discontinue study treatment

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MTX = methotrexate; LFT = liver function test; ULN = upper limit of normal.

13.5 Appendix 5: Tuberculosis Risk Questionnaires

13.5.1 Tuberculosis Risk Questionnaire for Screening Visit

The following questions are to be asked to every subject for evaluation of signs and symptoms of tuberculosis (TB). Responses to each question must be documented on this source document.

Question	Response
1) Does the subject have a currently active TB disease or a history of active TB disease?	☐ Yes ☐ No
2) Has the subject been in 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 the past 1.5 years?	☐ Yes ☐ No
3) Is the subject a TB hospital, forensic medical examination, or morgue employee?	☐ Yes ☐ No
4) Does the subject work or has the subject stayed in long-stay institutions (e.g., homes for the elderly or disabled, prisons, etc.)?	☐ Yes ☐ No
5) Does the subject reside in, did the subject ever reside in, or is the subject frequently travelling to a TB endemic region (as defined in Table 7)? (only applicable for subjects not living in an endemic region)	☐ Yes ☐ No
6) Is the subject in frequent contact with underprivileged populations (homeless people or other people needing social assistance)?	☐ Yes ☐ No
7) Does the subject have a new cough lasting more than 14 days or a change in a chronic cough?	☐ Yes ☐ No
8) Does the subject have night sweats?	☐ Yes ☐ No
9) Does the subject have a persistent fever?	☐ Yes ☐ No
10) Does the subject have unintentional weight loss (more than 10% of body weight) in the past 3 months?	☐ Yes ☐ No
11) Does the subject appear malnourished?	☐ Yes ☐ No
12) Has the subject had an abnormal chest X-ray since the last evaluation?	☐ Yes ☐ No

Physician's signature: _____

13.5.2 Tuberculosis Risk Questionnaire for Post-Screening Visits

The following questions are to be asked to every subject for evaluation of signs and symptoms of tuberculosis (TB). Responses to each question must be documented on this source document.

Question	Response
1) Does the subject have a new diagnosis of active TB disease?	☐ Yes ☐ No
2) Has the subject been in 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 since the last scheduled visit?	☐ Yes ☐ No
3) Has the subject become an employee of a TB hospital, forensic medical examiner, or morgue since the last scheduled visit?	☐ Yes ☐ No
4) Has the subject started work or has the subject stayed in long-stay institutions (e.g., homes for the elderly or disabled, prisons, etc.) since the last scheduled visit?	☐ Yes ☐ No
5) Does the subject reside in or is the subject frequently travelling to a TB endemic region (as defined in Table 7)? (only applicable for subjects not living in an endemic region)	☐ Yes ☐ No
6) Has the subject been in frequent contact with underprivileged populations (homeless people or other people needing social assistance) since the last scheduled visit?	☐ Yes ☐ No
7) Does the subject have a new cough lasting more than 14 days or a change in a chronic cough?	☐ Yes ☐ No
8) Does the subject have night sweats?	☐ Yes ☐ No
9) Does the subject have a persistent fever?	☐ Yes ☐ No
10) Does the subject have unintentional weight loss (more than 10% of body weight) in the past 3 months?	☐ Yes ☐ No
11) Does the subject appear malnourished?	☐ Yes ☐ No
12) Has the subject had an abnormal chest X-ray since the last evaluation?	☐ Yes ☐ No

Physician's signature: _____

Table 7 List of Endemic TB Countries (Incidence >50/100,000)

Country	Incidence[a]	Country	Incidence[a]	Country	Incidence[a]
Afghanistan	189 (167–212)	Greenland	197 (173–223)	Nigeria	322 (189–488)
Algeria	78 (64–94)	Guatemala	57 (51–64)	Northern Mariana Islands	61 (53–69)
Angola	370 (240–529)	Guinea	177 (156–199)	Pakistan	270 (201–350)
Azerbaijan	77 (68–86)	Guinea-Bissau	369 (261–495)	Papua New Guinea	417 (304–547)
Bangladesh	227 (200–256)	Guyana	103 (91–116)	Peru	120 (98–145)
Belarus	58 (50–67)	Haiti	200 (177–225)	Philippines	288 (254–324)
Benin	61 (50–74)	India	167 (156–179)	Romania	81 (71–91)
Bhutan	164 (148–181)	Indonesia	399 (274–546)	Russia	84 (76–93)
Bolivia	120 (106–135)	Ivory Coast	165 (150–179)	Rwanda	63 (54–72)
Botswana	385 (361–410)	Kazakhstan	99 (64–141)	Sao Tome and Principe	97 (85–109)
Brunei	62 (54–70)	Kenya	246 (240–252)	Senegal	138 (122–154)
Burkina Faso	54 (48–59)	Kiribati	497 (406–597)	Sierra Leone	310 (235–394)
Burundi	126 (116–136)	Kyrgyzstan	142 (126–160)	Solomon Islands	86 (71–102)
Cabo Verde	138 (122–156)	Laos	189 (141–244)	Somalia	274 (242–308)
Cambodia	390 (353–428)	Lesotho	852 (612–1130)	South Africa	834 (737–936)
Cameroon	220 (195–247)	Liberia	308 (273–346)	South Korea	86 (81–91)
Central African Republic	375 (333–420)	Lithuania	62 (57–68)	South Sudan	146 (121–173)
Chad	159 (141–179)	Madagascar	235 (207–264)	Sri Lanka	65 (57–73)
China	68 (63–73)	Malawi	227 (122–365)	Sudan	94 (52–148)
China, Hong Kong	74 (65–84)	Malaysia	103 (83–124)	Swaziland	733 (533–963)
China, Macao	82 (72–93)	Mali	58 (56–59)	Tanzania	327 (155–561)
Congo	381 (335–430)	Marshall Islands	335 (274–402)	Tajikistan	91 (80–103)

Country	Incidence[a]	Country	Incidence[a]	Country	Incidence[a]
Democratic Republic of Congo	325 (295–356)	Mauritania	111 (79–148)	Thailand	171 (90–276)
Djibouti	619 (547–696)	Micronesia	195 (87–347)	Timor-Leste	498 (411–594)
Dominican Republic	60 (53–68)	Moldova	153 (135–172)	Togo	58 (47–70)
Ecuador	54 (39–71)	Mongolia	170 (149–193)	Turkmenistan	64 (52–78)
Equatorial Guinea	162 (142–184)	Morocco	106 (97–115)	Tuvalu	190 (154–228)
Eritrea	78 (57–103)	Mozambique	551 (435–680)	Uganda	161 (141–183)
Ethiopia	207 (168–250)	Myanmar	369 (334–406)	Ukraine	94 (83–106)
Fiji	67 (55–81)	Namibia	561 (492–635)	Uzbekistan	82 (61–107)
Gabon	444 (393–497)	Nauru	73 (64–83)	Vanuatu	63 (52–74)
Gambia	174 (145–206)	Nepal	158 (139–178)	Vietnam	140 (116–167)
Georgia	106 (99–114)	Nicaragua	58 (53–63)	Yemen	48 (42–54)
Ghana	165 (80–281)	Niger	98 (87–110)	Zambia	406 (279–557)
				Zimbabwe	278 (193–379)

Abbreviations: HIV = human immunodeficiency virus; TB = tuberculosis; WHO = World Health Organization.

a. Rate per 100,000 population

Note: ranges represent uncertainty intervals.

Note: The 30 WHO TB high burden countries are as follows: Angola, Bangladesh, Brazil, Cambodia, China, Congo, Central African Republic, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Philippines, Russian Federation, Sierra Leone, South Africa, South Korea, Thailand, the United Republic of Tanzania, Viet Nam, Zambia, and Zimbabwe.

Source: WHO Global Tuberculosis Report 2015.

13.6 Appendix 6: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[a]
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

Abbreviations: BP = blood pressure; PEF = peak expiratory flow.

a. Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Reproduced from Sampson HA, et al. J Allergy Clin Immunol. 2006. Feb;117(2):391-7.

13.7 Appendix 7: Recommendations for Management of Latent Tuberculosis

Adapted CDC Recommendations for Management of Latent TB

Drug(s)	Duration	Interval	Comments
Isoniazid	9 months	Daily	Preferred treatment for: • Persons living with HIV • Children aged 2 to 11 • Pregnant women (with pyridoxine/vitamin B6 supplements)
		Twice weekly[a]	Preferred treatment for: • Pregnant women (with pyridoxine/vitamin B6 supplements)
Isoniazid	6 months	Daily	This regimen is not preferred for TB prophylaxis and should not be used in this study.
		Twice weekly[a]	
Isoniazid and Rifapentine	3 months	Once weekly[a]	Treatment for: • Persons 12 years or older Not recommended for persons who are: • Younger than 2 years old • Living with HIV/AIDS taking antiretroviral treatment • Presumed infected with INH or RIF-resistant *Mycobacterium tuberculosis* • Women who are pregnant or expect to become pregnant within the 12-week regimen
Rifampin	4 months	Daily	

Abbreviations: AIDS = acquired immunodeficiency syndrome; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; INH = isoniazid; RIF = rifampin; TB = tuberculosis.

a. Use Directly Observed Therapy (DOT).

13.8 Appendix 8: Protocol Amendment 1.1 Summary of Changes

SUMMARY OF RATIONALE AND CHANGES

Changes have been made to the Protocol CL04041022, Amendment 1.1. Based on the information presented in this amendment, there are no changes to the risk profile of olokizumab.

This amendment is specific to Russian Federation and Republic of Belarus

Study CL04041022 (CREDO 1) is being conducted in several countries including Russia, Belarus, Turkey and Bulgaria, and consistency of study design and conduct is maintained across all regions. However, it is important to ensure that the collected sample sets in pharmacokinetic subpopulation, which will be used further for calculation of Olokizumab pharmakoinetic parameters, is sufficient for appropriate analysis. As such this amendment is required to incorporate the possibility to increase the number of enrolled subjects in pharmacokinetic subpopulation in actively recruiting countries.

Individual revisions to the protocol are summarized below, with new text presented in **bold** font and deleted text presented in ~~strikethrough~~ font.

Minor misprintings and formatting changes have also been made throughout the protocol amendment.

INDIVIDUAL CHANGES

PROTOCOL LOCATION: *Synopsis (Pharmacokinetic Endpoints) and Section 4.4 Pharmacokinetic Endpoints*

CHANGE	Sample-rich PK subpopulation: **at least** 42 subjects in the PK subpopulation will be consented with an additional informed consent form (ICF) and serial blood samples will be collected following the first dose of study treatment (Week 0) and over a 4-week period at steady state (Weeks 20 through 24) **to reach appropriate number of the enrolled subjects for further analysis of PK parameters**.

PROTOCOL LOCATION: *Section 5.1 Summary of Study Design, Section 5.4.1.2 Randomisation (Visit 2, Week 0)*

CHANGE	The Schedule of Events to be conducted during the initial 24 week double-blind Treatment Period (Screening through Week 24) and the Safety Follow Up Period (Week 24 through Week 44) is presented in Table 1 for all subjects who are not part of the sample-rich PK subpopulation. For subjects who have consented in a separate, optional ICF to be included in the ~~PK subpopulation and are selected~~ ~~to be included in the~~ sample-rich PK subpopulation, the Schedule of Events is presented in Table 2.

PROTOCOL LOCATION: *Section 7.2 (Pharmacokinetiks)*

CHANGE

- Sample-rich PK subpopulation: **At least** 42 of the 140 consenting subjects in the PK subpopulation, **additional ICF will be consented and** serial blood samples will be collected following the first dose of study treatment (Week 0) and over a 4-week period at steady state (Weeks 20 through 24) **to reach appropriate number of the enrolled subjects for further analysis of PK parameters** . Olokizumab PK parameters will be determined by using noncompartmental analysis in subjects randomized to OKZ following single (Week 0) and multiple dose (Week 20) administration, as appropriate.
  - The IWRS will be constructed to select consenting subjects to be included in the PK subpopulation in a blinded fashion based on the group to which they are randomized.
  - Subjects in the sample-rich PK subpopulation should use the same SC injection site (either abdomen or thigh) to administer the study treatment at Visit 2 and Visit 13 unless otherwise

medically indicated.

All PK samples will be collected at the sampling times shown in Table 5. Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. Details on sample processing, handling, shipment, and storage are provided in a separate Laboratory Manual. Tubes and preprinted labels will be provided by the central laboratory to the study sites.

The following information will be captured for blood PK sample collection in each subject's eCRF:

- Patient number and initials
- Date and time of study treatment administration for the last 2 visits preceding the PK sample collection
- Date and time of the blood PK sample collection
- Date and time of study treatment administration on visit day of PK blood collection
- Sampling problems will be noted in the Comments section

The number of subjects included in the PK subpopulation is considered **to be** sufficient to describe individual OKZ PK following serial sample collections after the first dose of OKZ and at steady state, and to allow for assessment of accumulation after multiple-dose administration. Protocol deviations or events affecting the PK results may interfere with PK assessments. Prior to unblinding, deviations and other events will be reviewed to assess if they may affect PK. If a subject or sample has a deviation or event that may affect the interpretation of PK, the subject or sample may be excluded from the PK population or the PK analysis.

Assuming an approximately 15% rate of discontinuation after the first dose, serial OKZ concentrations **in PK sample-rich sub-population** are expected to be available for approximately 13 to 14 subjects per OKZ treatment group following the dose on Day 1 and **approximately** 11 to 12 subjects per OKZ treatment group at steady state.

PROTOCOL LOCATION: *Section 7.2 Table 5.* Sample Collection for PK, ADA, and Biomarker Assessments

CHANGE

Visit	Week	Dose	Time relative to OKZ dose[a]	Dedicated PK sample collection in PK subpopulation (approximately 140 subjects)		PK and ADA sample collection	Biomarker sample collection
				Sample-rich PK subpopulation (N≈42)	Remaining subjects (N≅98)	All subjects[b] (N=420)	Sample-rich PK subpopulation (N≅42)