

## Clinical Study Protocol

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<b>Protocol Title:</b>	<b>A Multicenter, Open-Label, Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis</b>
<b>Protocol Number:</b>	<b>CL04041024: Clinical Rheumatoid Arthritis Development for Olokizumab (CREDO) 4</b>
<b>Date of Protocol:</b>	<b>06 March 2019</b>
<b>Version of Protocol:</b>	<b>Amendment 2</b>
<b>Product:</b>	<b>Olokizumab (CDP6038; L04041)</b>
<b>IND No:</b>	<b>104933</b>
<b>EudraCT No:</b>	<b>2015-005309-35</b>
<b>Study Phase:</b>	<b>III</b>
<b>Sponsor:</b>	<b>R-Pharm International 19-1, Berzarina Street, Moscow Russian Federation 123154</b>

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### Confidentiality Statement

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The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. The acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from R-Pharm International.

## Signatures

**PROTOCOL TITLE:** A Multicenter, Open-Label, Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis

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**Mikhail Samsonov**

**Chief Medical Officer**

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**Signature**

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**Date**

## Investigator Signature Page

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This protocol is a confidential communication of R-Pharm International. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from R-Pharm International.

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 International'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	+1 512 652 0191 or  +1 973 659 6677 or  +3 318 699 0019
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 address:  QLS_Olokizumab@iqvia.com

Abbreviations: eCRF = electronic case report form; EDC = Electronic Data Capture; SAE = Serious Adverse Event.

## SYNOPSIS

<b>Name of Sponsor</b>	R-Pharm International	
<b>Name of Finished Product</b>	Olokizumab	
<b>Name of Active Ingredient</b>	Olokizumab (CDP6038; L04041)	
<b>Title of Study:</b>	A Multicenter, Open-label, Phase III Study of the Efficacy and Safety of Olokizumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis	
<b>Protocol No:</b>	CL04041024: Clinical Rheumatoid Arthritis Development for Olokizumab (CREDO) 4	
<b>Investigators:</b>	A total of approximately 250 Investigators will be involved in the conduct of this study.	
<b>Study sites:</b>	The study will be conducted at approximately 250 sites across Russia, Belarus, the United States (US), Europe, the United Kingdom, Asia, and Latin America.	
<b>Study duration:</b>	Treatment Period: 82 weeks Safety Follow-Up: 20 weeks	Phase: III
<b>Objectives:</b> <b>Primary:</b> The primary objective of this study is to evaluate the long-term safety and tolerability of olokizumab (OKZ) 64 mg administered subcutaneously (SC) once every 2 weeks (q2w) or once every 4 weeks (q4w) in subjects with moderately to severely active rheumatoid arthritis (RA) who previously completed 24 weeks of double-blind treatment in Study CL04041022, CL04041023, or CL04041025 (core studies). <b>Secondary:</b> <ul style="list-style-type: none"> <li>To evaluate the long-term efficacy of OKZ</li> <li>To evaluate the long-term immunogenicity of OKZ</li> <li>To evaluate the physical function and quality of life of subjects receiving long-term treatment with OKZ</li> </ul>		
<b>Criteria for Evaluation:</b> The following endpoints will be assessed to evaluate treatment with OKZ 64 mg administered SC q2w or q4w for 106 total weeks for subjects randomized to OKZ in all 3 core studies (CL04041022, CL04041023, and CL04041025), and for 82 total weeks for subjects randomized to placebo in the CL04041022 study and to placebo or adalimumab in the CL04041023 core study. In Study CL04041025, subjects randomized to placebo will transition to OKZ at Week 16 and complete 8 weeks of double-blind treatment with OKZ; these subjects will complete 90 total weeks of treatment with OKZ. <b>Safety Endpoints:</b> <ul style="list-style-type: none"> <li>The nature, incidence, severity, and outcome of adverse events (AEs), including serious adverse events (SAEs) and AEs of special interest (AESIs)</li> <li>Follow-up- adjusted incidence and event rates (per 100 subject-years of follow-up) for SAEs and AESIs</li> <li>Proportions of subjects with clinically significant laboratory abnormalities</li> <li>Assessment of changes over time in clinical laboratory parameters, vital sign measurements, and physical examination findings</li> <li>Time from first exposure to OKZ to the first occurrence of any major adverse cardiac event (MACE)</li> <li>Incidence and titer of antidrug antibodies (ADAs) to OKZ, incidence of neutralizing antibodies, and</li> </ul>		

the time course of antibodies

#### **Efficacy Endpoints:**

- Proportion of subjects achieving an American College of Rheumatology 20% (ACR20), American College of Rheumatology 50% (ACR50), and American College of Rheumatology 70% (ACR70) response who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Proportion of subjects with Simplified Disease Activity Index (SDAI)  $\leq 3.3$  remission, who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Proportion of subjects with Disease Activity Score 28-joint count (DAS28) low disease activity (based on DAS28 C-reactive protein [CRP]  $< 3.2$ ), who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Change from baseline over time in DAS28 (CRP), assessed at all applicable time points
- Change from baseline over time in the measure of physical ability based on Health Assessment Questionnaire-Disability Index (HAQ-DI), assessed at all applicable time points
- Proportion of subjects with improvement from baseline in HAQ-DI score  $\geq 0.22$ , who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Change from baseline over time in the scores for the following patient-reported outcomes (PRO) measures, assessed at all applicable time points:
  - 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 over time in SDAI and Clinical Disease Activity Index (CDAI), assessed at all applicable time points
- Proportion of subjects with moderate to good responses for European League Against Rheumatism (EULAR) based on DAS28 (CRP), who remain on randomized open-label treatment and in the study, assessed at all applicable time points, where a moderate response is defined as either DAS28 (CRP)  $\leq 5.1$  with an improvement from baseline in DAS28 (CRP)  $> 0.6$  and  $\leq 1.2$ , or DAS28 (CRP)  $> 3.2$  with an improvement from baseline in DAS28 (CRP)  $> 1.2$ , and a good response is defined as DAS28 (CRP)  $\leq 3.2$  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

#### **Immunogenicity:**

- Evaluating the impact of ADAs to OKZ on subject safety and efficacy

#### **Methodology:**

This OLE study (CL04041024) includes an 82-week open-label Treatment Period following completion of 1 of the core studies (Study CL04041022, CL04041023, or CL04041025) from Visit 1 (OLE Baseline/Week 24) to Visit 10 (End of Treatment [EoT]/Week 106), followed by a 20-week Safety Follow-Up Period from Week 106 to Week 126. The first visit of the OLE study is the same visit as the Week 24 visit in the core studies.

An estimated 1880 subjects will receive OKZ:

1. OKZ 64 mg q4w: SC injection of OKZ 64 mg q4w + methotrexate (MTX)
2. OKZ 64 mg q2w: SC injection of OKZ 64 mg q2w + MTX

Subjects will be randomized to 1 of the 2 OKZ treatment groups in the OLE study based on the treatment received in the core studies. Subjects who received OKZ (q2w or q4w) in the core study in which they participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ

at Week 16) will receive the same OKZ treatment regimen in the OLE study. Subjects who received placebo (Study CL04041022 and CL04041023) or adalimumab (Study CL04041023) in the core study in which they participated will be randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study.

For the first 12 weeks of the OLE, all subjects will be required to remain on a stable dose of background MTX at 15 to 25 mg/week (or  $\geq 10$  mg/week if there is documented intolerance to higher doses) with a stable route of administration (oral, SC, or intramuscular [IM]). After 12 weeks (Visit 4 [Week 36] of the OLE study), the Investigator may adjust the MTX dosage and route, per local guidelines. Methotrexate may be adjusted only for safety reasons according to Investigator discretion before Visit 4 (Week 36) of the OLE study.

Subjects who are on rescue disease-modifying anti-rheumatic drugs (DMARDs) during the core studies will be asked to continue these medications for the first 12 weeks of the OLE study. The Investigator can adjust these background medications if deemed appropriate after Visit 4 (Week 36) of the OLE study. Background rescue therapy may be adjusted only for safety reasons according to Investigator discretion before Visit 4 (Week 36) of the OLE study.

Throughout the study, concomitant treatment with folic acid  $\geq 5$  mg per week or equivalent is required for all subjects.

Subjects will return to the study site periodically for safety and response assessments as per the Schedule of Events.

The last dose of open-label study treatment in the OLE study will be administered at Week 104 for all subjects. After completion of the 82-week open-label Treatment Period, subjects will enter the 20-week Safety Follow-Up Period. During the Safety Follow-Up Period, subjects will return for 3 visits at +4, +8, and +22 weeks after the last dose of study treatment.

Subjects who discontinue the open-label treatment prematurely will be required to come for the EoT Visit 2 weeks after the last study treatment administration and then return for the 3 Safety Follow-Up Visits +4, +8, and +22 weeks after the last study treatment administration.

Adverse events will be assessed throughout the study period and evaluated using the Common Technology Criteria version 4.0 (CTCAE v 4.0).

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

<b>Planned number of subjects:</b>	Approximately 1880 subjects will be randomly assigned to 1 of 2 treatment groups (the OKZ 64 mg q4w treatment group or the OKZ 64 mg q2w treatment group).
<b>Treatment population:</b>	Subjects with moderately to severely active RA who previously completed 24 weeks of double-blind treatment in the core studies.
<b>Diagnosis and main criteria for inclusion:</b>	<ol style="list-style-type: none"> <li>1. Subjects willing and able to sign informed consent.</li> <li>2. Subject must have completed the 24-week double-blind Treatment Period in the core study.</li> <li>3. Subject must have maintained their stable dose (and route) of MTX 15 to 25 mg/week (or <math>\geq 10</math> mg/week if there is documented intolerance to higher doses) during the core study and plan to maintain the same dose and route of administration for <math>\geq 12</math> additional weeks.</li> </ol>
<b>Test product, dose and mode of administration:</b>	<p>Olokizumab is a humanized monoclonal antibody specific for interleukin-6 (IL-6).</p> <p>Subjects will be assigned to receive OKZ at 64 mg via SC injection either q2w or q4w.</p>

## **Statistical Methods:**

### **Calculation of Sample Size**

It is estimated that 1880 subjects will be enrolled in the OLE study after having completed a core study.

### **Analysis Populations**

- Safety population: The Safety population will include all subjects who receive at least 1 dose of study treatment during the OLE study. Subjects in the Safety population will be analyzed according to the treatment they actually received.
- Modified Intent-to-treat (mITT) population: The mITT population will include all subjects who sign an Informed Consent for participation in the OLE study, are randomized in the OLE study, and receive at least 1 dose of study treatment in the OLE study. Subjects will be analyzed according to the study treatment group to which they are randomized in the OLE study. The mITT population will be the primary efficacy analysis population.
- Per Protocol (PP) population: The PP population will include all mITT subjects who do not have any major protocol violations. Subjects will be analyzed according to the study treatment group to which they are randomized. The PP population will be used for supportive analyses selected efficacy endpoints.

### **Safety Analysis**

The main components for the safety analysis will include:

- All AEs (and SAEs) will be solicited at every study visit, recorded, and coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA)
- Vital signs and physical examination findings
- Laboratory parameters
- Electrocardiogram (ECG) and other specialized test findings

Changes from OLE Baseline value in safety parameters will be summarized based on the definition of OLE Baseline value as the last available measurement prior to the first OLE dose of study treatment. Additionally, changes from Core Baseline will be summarized based on the baseline value from the core study (i.e., the last available measurement prior to the first dose of study treatment in the core study). For subjects from Study CL04041025 who initiate OKZ treatment at Week 16 of the core study after having completed 16 weeks of placebo treatment, changes from the last pre-OKZ value will also be summarized.

All AEs will be analyzed in terms of descriptive statistics and qualitative analysis. Adverse events will be summarized in terms of incidence during the OLE study, as well as overall during the core studies and the OLE study. 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. Follow-up-adjusted incidence rates and event rates per 100 subject-years of follow-up over the course of the core study and the OLE will be summarized by treatment group for SAEs and AESIs. All safety and tolerability data recorded during the study will be listed and summarized by treatment group in both the core study and the OLE, and over time, as appropriate.

The above collected clinical database will be summarized and presented with particular focus on the following safety concerns identified as AESIs based either upon the safety data available to date (refer to the most recent version of the Investigator's Brochure) for OKZ or drug class-related events for a biologic, including IL-6 inhibitors:

- Infections (particularly serious infections), tuberculosis, opportunistic infections
- Malignancies
  - The Investigator will be asked to provide relevant medical information/documentation (e.g., pathology/histology reports) on all the malignancies 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, elevation of low-density lipoprotein [LDL])
- Systemic injection reactions and hypersensitivity reactions, including anaphylaxis
- Gastrointestinal perforation
- Cardiovascular (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
- Injection site reactions
- Demyelination in peripheral or central nervous system
- Autoimmune disorders

#### **Cardiovascular Risk Assessment**

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

- Potential 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.
- Baseline (of the core study) CV risks including individual risk factors (e.g., tobacco use, presence of hypertension, diabetes mellitus, and lipid profile) will be assessed.
- Known CV risk factors will be monitored and assessed to detect any trends over long-term exposure.

Time from first exposure to OKZ treatment (either in the core study or OLE study) to first adjudicated MACE event will be summarized using the Kaplan-Meier methodology by treatment group.

#### **Efficacy Analysis**

Efficacy analyses will be conducted using the mITT population. Changes from OLE Baseline value in efficacy parameters will be summarized based on the definition of OLE Baseline value as the last available measurement prior to the first OLE dose of study treatment. Additionally, changes from Core Baseline will be summarized based on the baseline value from the core study (i.e., the last available measurement prior to the first dose of study treatment in the core study). For subjects from Study CL04041025 who initiate OKZ treatment at Week 16 of the core study after having completed 16 weeks of placebo treatment, changes from the last pre-OKZ value will also be summarized. There will be no inferential comparisons between treatment groups for efficacy assessments. Descriptive summaries will be provided for each efficacy parameter over time by treatment group.

#### **Assessment of Nonresponders**

Starting at Visit 4 (Week 36) and then at all onsite visits until the end of the open-label Treatment Period, all subjects will be assessed for response to treatment, with nonresponders defined as subjects who do not improve by at least 20% in swollen and tender joint counts (66-68 joint assessment) from the Core Baseline assessment. Investigators will be requested to review carefully the response status at these time points and make appropriate actions based on local guidelines regarding management of the subjects, including possible adjustments in background therapy or withdrawal from the study.

#### **Safety Follow-up Assessments**

Given the long half-life of OKZ (approximately 31 days), a 2-step approach to fully capture the safety data after subjects discontinue treatment is proposed. First, this Phase III study requires a full safety assessment at the EoT Visit, which will take place 2 weeks after the last dose of study treatment. For subjects remaining on open-label therapy until the last scheduled dose of study treatment, Visit 10 (the EoT Visit) will take place at Week 106. For subjects who discontinue treatment prematurely, the EoT Visit will take place 2 weeks after the

last study treatment administration. Second, subjects will also be followed up for approximately 5 OKZ half-lives (i.e., 22 weeks) after the final dose of study treatment. Specifically, after the EoT Visit, all subjects will be scheduled for extended Safety Follow-Up Visits at +4, +8, and +22 weeks after the last dose of study treatment. 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.

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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
ApoB	apolipoprotein B
ApoA1	apolipoprotein A1
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Class
bDMARD	biologic disease-modifying anti-rheumatic drug
BNP	brain natriuretic peptide
BP	blood pressure
CDAI	Clinical Disease Activity Index
CDC	Centers for Disease Control and Prevention
cDMARD	conventional disease-modifying anti-rheumatic drug
CDR	complementarity determining region
CMF	cumulative mean function
CRP	C-reactive protein
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

<b>Abbreviation</b>	<b>Definition</b>
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
ER	event rate
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
gp80	interleukin-6 receptor alpha chain
gp130	interleukin-6 receptor signal-transducing subunit
HAQ-DI	Health Assessment Questionnaire - Disability Index
HbA <sub>1c</sub>	glycosylated hemoglobin
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IA	intra-articular
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IM	intramuscular
INR	international normalized ratio
IP	interphalangeal(s)
IR	incidence rate
IRB	Institutional Review Board

<b>Abbreviation</b>	<b>Definition</b>
ISS	Integrated Summary of Safety
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
mAb	monoclonal antibody
MACE	major adverse cardiac event
MCP	metacarpophalangeal
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MTP	metatarsophalangeals
MTX	methotrexate
n	number of available values
NOAEL	no observed adverse effect level
NSAID	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
PFS	pre-filled syringe(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

<b>Abbreviation</b>	<b>Definition</b>
RA	rheumatoid arthritis
RBC	red blood count
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
SY	subject-years
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF- $\alpha$	tumor necrosis factor- $\alpha$
TNFi	tumor necrosis factor- $\alpha$ inhibitor
ULN	upper limit of normal
UK	United Kingdom
US	United States
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 patients 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- $\alpha$  (TNF- $\alpha$ ) 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 patients with established RA fail to respond and 50% to 60% of patients 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 International for the treatment of moderately to severely active RA. Olokizumab was previously developed by UCB Pharma SA, and was transferred to R-Pharm International 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- $\alpha$ , 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 nonsignaling IL-6R receptor 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 that inhibit TNF- $\alpha$ , 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 and improve physical functioning. 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 or previous TNFi treatment.

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
- Pharmacokinetics, 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 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 subjects (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  $\geq 3\%$  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 SOC 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 SOC 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  $\geq 10\%$  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 ( $\geq 59.1\%$ ) 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 SOC 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  $\geq 2$  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 SOC 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 ( $\geq 56.3\%$ ) 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 SOC of infections and infestations; GI disorders; general disorders and administration site condition; skin and SC 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 that 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 that 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 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. These are the same doses investigated in the 3 core studies (CL04041022, CL04041023, and CL04041025). The rationale for selecting these dose regimens 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 1 or more TNFi biologics, the 60 mg monthly treatment 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 that 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 the 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 multicenter, open-label design used in this study is consistent with the precedent set for Phase III OLE trials of other biologics and is in accordance with health authority guidelines.

The goal of this Phase III study is to evaluate the long-term safety, tolerability, and efficacy of OKZ in subjects with moderately to severely active RA who previously completed

24 weeks of double-blind treatment with OKZ in the core studies. Olokizumab is expected to reduce the disease activity and induce an improvement in physical function. The study is expected to provide long-term safety information in a large group of subjects treated with OKZ for up to 106 weeks.

All subjects in this study will receive the first dose of OKZ at Week 24. For subjects transitioning from the adalimumab treatment group (core study CL04041023), there will be no additional time added for wash out of adalimumab other than the 2 weeks between the last dose of adalimumab in the core study (Week 22) and first dose of OKZ in the OLE study (Visit 1 [Week 24]). Similar approaches have been implemented in a number of other clinical studies involving adalimumab and other biologics or kinase inhibitors, and such a switch from one biologic to another is commonly observed in clinical practice without significant safety concerns (Bykerk et al, 2012; Furst et al, 2007; Schiff et al, 2009; Wollenhaupt et al, 2014). Despite this, the possibility for an increased risk of AEs, including infections, cannot be excluded (Humira® [adalimumab] Prescribing Information). This potential risk will be mitigated by closely monitoring all subjects throughout the OLE study.

It is possible that subjects assigned to the adalimumab treatment group in core study CL04041023 might achieve remission or a decrease in disease activity while being treated with adalimumab and switching to another biological treatment may lead to undesirable results for such subjects. However, it will not be known at the completion of the 24-week double-blind Treatment Period whether a subject was assigned to the adalimumab treatment group. Therefore, following a subject's completion of the core study and prior to enrollment in the OLE study, the Investigator and subject will decide jointly whether the subject will continue with the open-label administration of OKZ in this OLE study or exit the study.

## **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 (Studies 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, and tolerability 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. All subjects will be eligible for modification of background therapy (i.e., MTX for all subjects, sulfasalazine and/or hydroxychloroquine for subjects assigned rescue medication in the core studies, and oral corticosteroids [if applicable]), administration of parenteral corticosteroids, and modification of non-steroidal anti-inflammatory drugs (NSAIDs) after 12 weeks of open-label treatment (see Section 6.13.3), according to Investigator discretion and local practice. In addition, all subjects will be assessed at Visit 4 (Week 36) and then at all onsite visits until the end of the study treatment administration for response to treatment, with nonresponders defined as subjects who do not improve by at least 20% in swollen and tender joint counts (66-68 joint assessment) from the Core Baseline assessment. Investigators will be requested to review carefully the response status at these time points and make appropriate actions based on local guidelines regarding management of the subjects, including possible adjustments in background therapy or withdrawal from the study.

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 the anticipated efficacy/benefit remains favorable.

### **3. STUDY OBJECTIVES**

#### **3.1 Primary Objective**

The primary objective of this study is to evaluate the long-term safety and tolerability of OKZ 64 mg administered SC q2w or q4w in subjects with moderately to severely active RA who previously completed 24 weeks of double-blind treatment in the core studies.

#### **3.2 Secondary Objectives**

The secondary objectives of this study are as follows:

- To evaluate the long-term efficacy of OKZ
- To evaluate the long-term immunogenicity of OKZ
- To evaluate the physical function and quality of life of subjects receiving long-term treatment with OKZ



## 4. SUMMARY OF STUDY ENDPOINTS

The following safety, efficacy, and immunogenicity endpoints will be assessed to evaluate long-term treatment with OKZ 64 mg q2w or OKZ 64 mg q4w.

### 4.1 Safety Endpoints

The following safety endpoints will be evaluated:

- Nature, incidence, severity, and outcome of AEs, including SAEs and AEs of special interest (AESIs)
- Follow-up-adjusted incidence rates (IR) and event rates (ER) (per 100 subject-years [SY] of follow-up) for SAEs and AESIs
- Proportions of subjects with clinically significant laboratory abnormalities
- Assessment of changes over time in clinical laboratory parameters, vital sign measurements, and physical examination findings
- Time from first exposure to OKZ to the first occurrence of any major adverse cardiac event (MACE)
- Incidence and titer of antidrug antibodies (ADAs) to OKZ, incidence of neutralizing antibodies, and the time course of antibodies

### 4.2 Efficacy Endpoints

For the efficacy endpoints, comparison will be made with Core Baseline values (i.e., Week 0 baseline values in the core study) and OLE Baseline values (i.e., Week 24 baseline values in the OLE study) for most parameters, as defined in Section 9.4.1. For subjects from Study CL04041025 who initiate OKZ treatment at Week 16 of the core study after having completed 16 weeks of placebo treatment, changes from the last pre-OKZ value will also be summarized.

The following efficacy endpoints will be evaluated:

- Proportion of subjects achieving an ACR20, ACR50, and ACR70 response who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Proportion of subjects with Simplified Disease Activity Index (SDAI)  $\leq 3.3$  remission, who remain on randomized open-label treatment and in the study, assessed at all applicable time points

- Proportion of subjects with Disease Activity Score 28-joint count (DAS28) low disease activity (based on DAS28 C-reactive protein [CRP]  $<3.2$ ), who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Change from baseline over time in DAS28 (CRP), assessed at all applicable time points
- Change from baseline over time in the measure of physical ability based on Health Assessment Questionnaire-Disability Index (HAQ-DI), assessed at all applicable time points
- Proportion of subjects with improvement from baseline in HAQ-DI score  $\geq 0.22$ , who remain on randomized open-label treatment and in the study, assessed at all applicable time points
- Change from baseline over time in the scores for the following patient-reported outcomes (PRO) measures, assessed at all applicable time points:
  - 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 over time in SDAI and Clinical Disease Activity Index (CDAI), assessed at all applicable time points
- Proportion of subjects with moderate to good responses for EULAR based on DAS28 (CRP), who remain on randomized open-label treatment and in the study, assessed at all applicable time points, where a moderate response is defined as either DAS28 (CRP)  $\leq 5.1$  with an improvement from baseline in DAS28 (CRP)  $>0.6$  and  $\leq 1.2$ , or DAS28 (CRP)  $>3.2$  with an improvement from baseline in DAS28 (CRP)  $>1.2$ , and a good response is defined as DAS28 (CRP)  $\leq 3.2$  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

### **4.3 Immunogenicity**

The following immunogenicity endpoint will be evaluated:

- Impact of ADAs to OKZ on subject safety and efficacy

## 5. INVESTIGATIONAL PLAN

### 5.1 Summary of Study Design

This is a multicenter, open-label, Phase III study that will evaluate the efficacy and safety of OKZ in subjects with moderately to severely active RA who previously completed 24 weeks of double-blind treatment in Study CL04041022, CL04041023, or CL04041025.

This study will be conducted at approximately 250 global sites across Russia, Belarus, the US, Europe, the United Kingdom (UK), Asia, and Latin America. It is estimated that approximately 1880 subjects will be enrolled.

Subjects will be assessed for eligibility to enter the study at Visit 1 (which is the same visit as the Week 24 visit of the core studies), and eligible subjects will be assigned to 1 of 2 dosing frequencies (q2w or q4w) of 64 mg OKZ as described in Section 5.2.

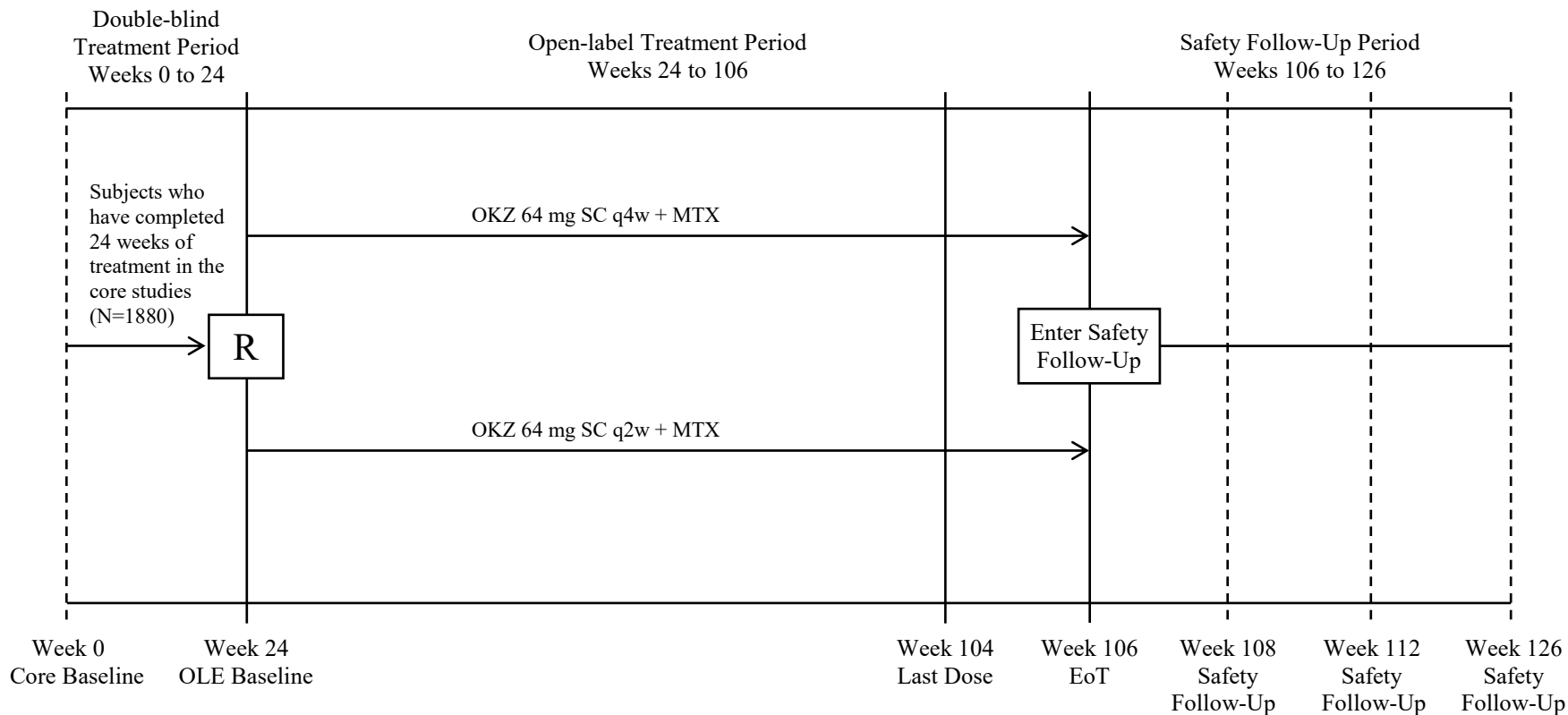
The study will consist of an 82-week open-label Treatment Period, with the last dose of OKZ being administered at Week 104. After completion of the open-label Treatment Period, subjects will come to Visit 10 (End of Treatment [EoT]/Week 106) 2 weeks after the last dose of OKZ for scheduled safety and efficacy assessments. After Visit 10 (EoT/Week 106), subjects will be scheduled for Safety Follow-Up Visits SFU-1 (Week 108), SFU-2 (Week 112), and SFU-3 (Week 126) to perform adequate safety assessments.

The total amount of time to complete the OLE study will be approximately 102 weeks (inclusive of the open-label Treatment Period and the Safety Follow-Up Period). The total amount of time to complete both the core study and the OLE study will be approximately 130 weeks (2.5 years) (inclusive of the Screening, double-blind Treatment Period, open-label Treatment Period, and Safety Follow-Up Period).

Subjects who discontinue treatment prematurely will be required to come to Visit 10 (EoT/Week 106) 2 weeks after the last dose of study treatment for scheduled efficacy and safety assessments. These subjects will subsequently be followed for an additional 20 weeks (i.e., 22 weeks after the final dose of study treatment) during a Safety Follow-Up Period.

A schematic of the study design is presented in Figure 1. The Schedule of Events to be conducted during the 82-week open-label Treatment Period (Week 24 through Week 106) and the Safety Follow-Up Period (Week 106 through Week 126) is presented in Table 1.

**Figure 1 CL04041024 (CREDO 4) Study Schematic**



Abbreviations: EoT = End of Treatment; MTX = methotrexate; N = total number of subjects; OKZ = olokizumab; OLE = open-label extension; q2w = once every 2 weeks; q4w = once every 4 weeks; R = randomization; SC = subcutaneous(ly).

**Table 1 CL04041024 (CREDO 4) Schedule of Events (Open-Label Treatment Period and Safety Follow-Up Period)**

Assessments	OLE Baseline	Open-Label Treatment Period								EoT	Safety Follow-Up Period		
Visit	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	SFU-1	SFU-2	SFU-3
Week	24	26	28	36	44	52	64	76	88	106 (+2 <sup>b</sup> )	108 (+4 <sup>b</sup> )	112 (+8 <sup>b</sup> )	126 (+22 <sup>b</sup> )
Visit Window (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7
Obtain informed consent	✓												
Determine eligibility for OLE	✓												
Height	✓												
Weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓ <sup>c</sup>	✓	✓	✓	✓	✓ <sup>c</sup>	✓	✓	✓	✓ <sup>c</sup>	✓	✓	✓ <sup>c</sup>
Vital signs <sup>d</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Contraceptive history/status	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant and prior medications/non-drug therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization	✓												
Training for study treatment administration <sup>e</sup>	✓	✓	✓										
Study treatment allocation through IWRS	✓	✓ <sup>f</sup>	✓	✓	✓	✓	✓	✓	✓				
Administer study treatment <sup>g,h</sup>	✓ <sup>i,j</sup>	✓ <sup>f,i,j</sup>	✓ <sup>i,j</sup>	✓	✓	✓	✓	✓	✓				
Study treatment compliance <sup>k</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
<b>EFFICACY ASSESSMENTS</b>													
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) <sup>l</sup>	✓			✓	✓	✓	✓	✓	✓	✓			
Assessment of nonresponders <sup>l</sup>				✓	✓	✓	✓	✓	✓	✓			

Assessments	OLE Baseline	Open-Label Treatment Period								EoT	Safety Follow-Up Period		
Visit	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	SFU-1	SFU-2	SFU-3
Week	24	26	28	36	44	52	64	76	88	106 (+2 <sup>b</sup> )	108 (+4 <sup>b</sup> )	112 (+8 <sup>b</sup> )	126 (+22 <sup>b</sup> )
Visit Window (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7
Physician Global Assessment (VAS)	✓			✓	✓	✓	✓	✓	✓	✓			
CRP	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	
ESR	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	
<b>Safety Assessments</b>													
AEs/SAEs <sup>n</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IGRA <sup>o</sup>						✓				✓			
Pregnancy test <sup>p</sup>	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
INR, aPTT, fibrinogen <sup>q</sup>	✓							✓		✓			✓
Lipid panel (fasting) <sup>r</sup>	✓					✓		✓		✓			✓
CV risk panel <sup>s</sup>	✓							✓		✓			✓
CV risk assessment <sup>t</sup>	✓					✓		✓		✓			
Hematology <sup>u</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chemistry panel <sup>v</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HbA <sub>1c</sub> <sup>w</sup> (only for subjects with diabetes mellitus)		✓				✓		✓		✓			
Urinalysis <sup>x</sup>	✓			✓		✓		✓		✓			✓
PK blood samples	✓ <sup>y</sup>												
ADAs	✓			✓		✓		✓		✓			
ANA and anti dsDNA antibody	✓					✓				✓			✓
Assess injection site reactions	✓	✓	✓	✓	✓	✓	✓	✓	✓				
TB risk questionnaire	✓			✓		✓		✓		✓		✓	
Chest X-ray <sup>z</sup>	✓					✓				✓			
12-lead ECG	✓					✓		✓		✓			✓

Assessments	OLE Baseline	Open-Label Treatment Period								EoT	Safety Follow-Up Period		
Visit	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	SFU-1	SFU-2	SFU-3
Week	24	26	28	36	44	52	64	76	88	106 (+2 <sup>b</sup> )	108 (+4 <sup>b</sup> )	112 (+8 <sup>b</sup> )	126 (+22 <sup>b</sup> )
Visit Window (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	±7
Subject Diary <sup>aa</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			

Abbreviations: ADA = antidrug antibody; AEs = adverse events; ALT = alanine aminotransferase; ANA = antinuclear antibody; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BP = blood pressure; 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<sub>1c</sub> = glycosylated hemoglobin; HDL = high-density lipoprotein; 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; OKZ = olokizumab; OLE = open-label extension; PFS = pre-filled syringe(s); PK = pharmacokinetic(s); PRO = patient-reported outcomes; RBC = red blood count; SAE = serious adverse event; SC = subcutaneous(ly); SF-36 = Short Form-36; SJC = swollen joint count; TB = tuberculosis; TJC = tender joint count; WBC = white blood count; WPS-RA = Work Productivity Survey – Rheumatoid Arthritis; VAS = Visual Analog Scale.

- All subjects will begin the OLE study at Visit 1. The baseline visit for the OLE study is the same visit as the Week 24 visit in the core studies.
- The number of weeks (+2, +4, +8, or +22) after the last dose of the study treatment.
- Complete physical examination should be performed at these visits (Section 7.4.7.1).
- Vital signs include temperature, heart rate, BP, and respiratory rate.
- Subjects (and their caregivers, if applicable) will be trained to administer the study treatment at Visit 1, and the Investigator must observe the first 2 administrations (Visits 1 and 2 for subjects receiving OKZ 64 mg q2w or Visits 1 and 3 for subjects receiving OKZ 64 mg q4w) to ensure that proper procedures are followed. This training may be repeated at any visit to the study site if requested by the subject or caregiver, or if deemed appropriate by the Investigator.
- Study treatment allocation and administration at Visit 2 (Week 26) is only for subjects assigned to the OKZ 64 mg q2w treatment group.
- If desired, SC injections may be rotated among the thighs and abdomen.
- Study treatment will be administered every 2 or 4 weeks (according to assigned OKZ treatment regimen) through the last dose of study treatment at Week 104 (not shown on this Schedule of Events).
- Subjects will remain at the study site for at least 2 hours after the first injection of study treatment (Visit 1 [OLE Baseline/Week 24]) and for at least 30 minutes after the second administration of study treatment (Visit 2 [Week 26] for subjects receiving OKZ 64 mg q2w and Visit 3 [Week 28] for subjects receiving OKZ 64 mg q4w) to be assessed for the onset of any systemic injection reactions (see Section 7.4.3.2 and Appendix 3 [Section 13.3]).
- Administration of study treatment must be observed by the Investigator for the first 2 administrations of OKZ 64 mg q2w (Visit 1 [Week 24] and Visit 2 [Week 26]) or OKZ 64 mg q4w (Visit 1 [Week 24] and Visit 3 [Week 28]).
- Starting from Visit 4 (Week 36), subjects must return to the study site either all used and unused vials of study treatment or empty cartons of used PFS and unused PFS at each scheduled visit. Compliance will be assessed by the Investigator based on the number of used vials or PFS cartons as applicable.



- 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 SJC and TJC. To ensure consistent joint evaluation throughout the study, individual subjects should be evaluated by the same joint assessor as in the core studies for all study visits whenever possible.
- m. Starting at Visit 4 (Week 36) and then at all onsite visits until the end of the open-label Treatment Period (Visit 10 [EoT/Week 106]), all subjects will be assessed for response to treatment, with nonresponders defined as subjects who do not improve by at least 20% in SJC and TJC (66-68 joint assessment) from the Core Baseline assessment.
- n. Adverse events and SAEs are reported from OLE Baseline.
- o. At scheduled visits, IGRA testing should be performed only for subjects who had a negative IGRA result at the previous assessments (including Week 22 assessment of the core study) unless other approach is required by local practice.
- p. Required for females of childbearing potential only. May be repeated more frequently (i.e., between study visits) if required by local practices, IRB/IECs or local regulations, if a menstrual cycle is missed, or if potential pregnancy is otherwise suspected. If more frequent testing is required, the study site will provide the patient with further guidance and a home testing kit.
- q. Samples for INR, aPTT, and fibrinogen should be collected prior to all other blood samples.
- r. Lipid panel includes total cholesterol, HDL, LDL, triglycerides, lipoprotein (a), apolipoproteins (ApoB, ApoA1, and ApoB:ApoA1 ratio), and adiponectin.
- s. Cardiovascular risk panel includes NT-proBNP, BNP, and homocysteine.
- t. Cardiovascular risk assessment includes alcohol use with an evaluation of average number of drinks consumed weekly, tobacco use with an evaluation of average number of tobacco products consumed daily, central obesity, use of any lipid-lowering medication or any other CV agents, prior history of CV events and diabetes, family history of premature CV disease (age <55 years for males and <65 years for females), and other risks.
- u. Hematology includes RBC, WBC with differential, hemoglobin, hematocrit, and platelet count.
- v. At all visits, subjects must attend study sites after fasting for at least 9 hours (water and concomitant medications are permitted). Chemistry panel includes urea nitrogen, creatinine, fasting glucose, calcium, sodium, potassium, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, and albumin.
- w. Glycosylated hemoglobin will be assessed at Visits 2, 6, 8, and 10 only for subjects with a confirmed diagnosis of diabetes mellitus prior to Visit 2 (Week 26). If a diagnosis of diabetes mellitus is confirmed after Visit 2 (Week 26), then HbA<sub>1c</sub> will be assessed at all subsequent visits as indicated in the Schedule of Events.
- x. Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.
- y. The Visit 1 (OLE Baseline/Week 24) PK samples are the last samples to be collected in the core studies. These samples must be collected prior to administration of OKZ, and the samples will be analyzed and included in the data set of the core study in which the subject participated, according to the procedures detailed in the core study protocol. The PK sample will not be analyzed as part of the OLE data set.
- z. If chest X-ray (both posteroanterior and lateral) was performed within 8 weeks, the assessment should not be repeated at the scheduled visit.
- aa. At Visit 1 (OLE Baseline/Week 24), Subject Diary will be distributed, and subjects will be trained to properly complete the Subject Diary. At Visit 1 (OLE Baseline/Week 24) and at each scheduled visit during the open-label Treatment Period (Visits 2 through 9), the Investigator will provide the subject with preprinted dates for each dose of study treatment that will be administered prior to the next scheduled visit. Following each administration of study treatment, the subject will record the date, time, and location of each study treatment administration; the identity of the person who administered the study treatment; any problems experienced during the injection; and any complaints, signs, or symptoms that occur during or after the injection. Investigators will collect and review the Subject Diary at Visits 2 (Week 26) through 10 (EoT/Week 106).

## 5.2 Discussion of Study Design

After completing the 24-week double-blind Treatment Period in 1 of the 3 core studies, an estimated 1880 subjects will be randomized to 1 of 2 open-label treatment groups:

1. OKZ 64 mg q4w: SC injection of OKZ 64 mg q4w + MTX
2. OKZ 64 mg q2w: SC injection of OKZ 64 mg q2w + MTX

Subjects will be randomized based on the treatment received in the core studies. Subjects who received OKZ (q2w or q4w) in the core study in which they participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) will receive the same OKZ treatment regimen in the OLE study. Subjects who received placebo (Study CL04041022 and Study CL04041023) or adalimumab (Study CL04041023) in the core study in which they participated will be randomized in a 1:1 ratio to OKZ 64 mg q2w or OKZ 64 mg q4w regimens in the OLE study.

The total duration of OKZ treatment will depend on the subject's treatment assignment in the core studies:

- Subjects randomized to OKZ in the 3 core studies (CL04041022, CL04041023, and CL04041025) will complete 106 total weeks of treatment with OKZ.
- Subjects randomized to placebo in Study CL04041022 and to placebo or adalimumab in Study CL04041023 will complete 82 total weeks of treatment with OKZ.
- Subjects randomized to placebo in Study CL04041025 will transition to OKZ at Week 16 and complete 8 weeks of double-blind treatment with OKZ during the core study; these subjects will complete 90 total weeks of treatment with OKZ.

Subcutaneous injections of OKZ 64 mg will be administered q2w or q4w throughout the open-label Treatment Period, and all subjects (and their caregivers, if applicable) will be trained at Visit 1 (OLE Baseline/Week 24) to administer OKZ (see Section 6.8).

Administration of study treatment will be observed by study site staff during the first 2 scheduled visits (Visit 1 [Week 24] and Visit 2 [Week 26] for subjects receiving OKZ 64 mg q2w, and Visit 1 [Week 24] and Visit 3 [Week 28] for subjects receiving OKZ 64 mg q4w). Detailed guidance on study treatment administration procedures will be provided in the Pharmacy Manual and Subject Leaflet.

For the first 12 weeks (up to Visit 4 [Week 36]) of the open-label Treatment Period, all subjects will be required to remain on a stable dose of background MTX at 15 to 25 mg/week (or  $\geq 10$  mg/week if there is documented intolerance to higher doses) with a stable route of

administration (oral, SC, or intramuscular [IM]), and subjects who were assigned rescue medication (sulfasalazine and/or hydroxychloroquine) in the core studies will be asked to continue these medications without a change in dose. Background therapy may be adjusted only for safety reasons according to Investigator discretion before Visit 4 (Week 36) of the OLE study.

Throughout the study, concomitant treatment with folic acid  $\geq 5$  mg per week or equivalent is required for all subjects.

The Investigator may, at their discretion and based on local practice, adjust therapy after Visit 4 (Week 36) (see Section 6.13.3), which may include adjustments to background therapy (i.e., MTX for all subjects, sulfasalazine and/or hydroxychloroquine for subjects assigned rescue medication in the core studies, and oral corticosteroids [if applicable]), parenteral corticosteroids, and modification of NSAIDs.

Dose tapering of oral corticosteroids or NSAIDs is permitted according to Investigator discretion before Visit 4 (Week 36) (see Section 6.13.3).

Subjects will return to the study site periodically for safety and response assessments as per Table 1. Adverse events will be assessed throughout the study period and evaluated using the CTCAE version 4.0.

The last dose of open-label study treatment in the OLE study will be administered at Week 104. After completion of the 82-week, open-label Treatment Period, subjects will enter the 20-week Safety Follow-Up Period. During the Safety Follow-Up Period, subjects will return for 3 visits at +4, +8, and +22 weeks after the last dose of study treatment.

Subjects who discontinue study treatment prematurely will be required to come to Visit 10 (EoT/Week 106) 2 weeks after the last dose of the study treatment for scheduled assessments. These subjects will subsequently be followed for an additional 20 weeks (i.e., 22 weeks after the final dose of study treatment) for a Safety Follow-Up Period.

There will be ongoing monitoring of safety events, including laboratory findings, by R-Pharm International or its designee. In addition, safety will be assessed throughout the study by an independent Data Safety Monitoring Board (DSMB) (see Section 7.4.4 for further details).

### **5.2.1 Cardiovascular Risk Assessment**

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

1. Potential 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 (of the core study) 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. A CV risk assessment will be performed at OLE Baseline and at Visits 6 (Week 52), 8 (Week 76), and 10 (EoT/Week 106). The CV risk assessment includes:
  - Alcohol use with evaluation of average number of drinks consumed weekly
  - Tobacco use with evaluation of average number of tobacco products consumed daily
  - Central obesity
  - Use of any lipid-lowering medication or any other CV agents
  - Prior history of CV events and diabetes
  - Family history of premature CV disease (age of diagnosis <55 years for males and <65 years for females)
  - Other risks

Cardiovascular risk assessment data will be provided to the CVAC for review and adjudication of MACE (see Section 7.4.4.2).

### **5.2.2 Safety Follow-up Assessments**

Given the long half-life of OKZ (approximately 31 days), 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, Visit 10 (EoT Visit) will be performed at Week 106 and extended Safety Follow-Up procedures will be performed at visits scheduled +4, +8, and +22 weeks after the last dose of study treatment (i.e., Visits SFU-1 [Week 108], SFU-2 [Week 112], and SFU-3 [Week 126], respectively).

Subjects who discontinue treatment early require a full safety assessment at Visit 10 (EoT/Week 106) (see Section 5.4.2), which will take place 2 weeks after the last study

treatment administration. These subjects will subsequently be followed for an additional 20 weeks (i.e., 22 weeks after the final dose of study treatment) during a Safety Follow-Up Period (see Section 5.4.3).

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 (Section 7.4.5.4).

### **5.3 Selection of Study Population**

The study population will consist of subjects with moderately to severely active RA who previously completed 24 weeks of double-blind treatment in one of the core CREDO studies.

This is an international study, and it is expected that approximately 1880 subjects will be randomized at approximately 250 sites across Russia, Belarus, the US, Europe, UK, Asia, and Latin America.

#### **5.3.1 Inclusion Criteria**

Subjects may be enrolled in the study only if they meet all of the following criteria:

1. Subject must be willing and able to sign informed consent
2. Subject must have completed the 24-week double-blind Treatment Period in 1 of the 3 core studies (CL04041022, CL04041023, or CL04041025).
3. Subject must have maintained their stable dose (and route) of MTX 15 to 25 mg/week (or  $\geq 10$  mg/week if there is documented intolerance to higher doses) during the core study and plan to maintain the same dose and route of administration for  $\geq 12$  additional weeks.
4. Subjects must be willing to take folic acid or equivalent throughout the study.

#### **5.3.2 Exclusion Criteria**

Subjects who meet any of the following criteria will not be eligible for the study:

1. Subject with any medically important condition in the core study (e.g., clinically significant laboratory values, frequent AEs or SAEs, infection SAEs, and/or other concurrent severe and/or uncontrolled medical condition) which would make this subject unsuitable for inclusion in the OLE study in the Investigator's judgement.
2. Subject has evidence of active TB
3. Subject with a positive or repeated indeterminate interferon-gamma release assay (IGRA) result at Week 22 of the core study

- Subjects may be enrolled in the OLE study if they fulfill all 3 of the following criteria prior to the first dose of study treatment:
  - a. 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);
  - b. The subject starts prophylaxis for latent TB infection (LTBI) according to country-specific/Centers for Disease Control and Prevention (CDC) guidelines (see Appendix 4 [Section 13.4]) (treatment with isoniazid for 6 months is not an appropriate prophylactic regime for this study and it should not be used); and
  - c. The subject is willing to complete the entire course of recommended LTBI therapy (see Appendix 4 [Section 13.4]).
- 4. Subject has planned surgery during the first 12 weeks of the OLE study
- 5. Female subjects who are pregnant or lactating, or who are planning to become pregnant during the study or within 6 months of the last dose of study treatment
- 6. 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 core study
  - 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 the first dose of study treatment in the core study (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, or diaphragm with spermicide) in combination with the following: established oral, injected, or implanted hormone methods of contraception or contraceptive patch
7. Subject is unwilling or unable to follow the procedures outlined in the protocol
8. Other medical or psychiatric conditions, or laboratory abnormalities that may increase the potential risk associated with study participation and administration of the study treatment, or that may affect study results interpretation and, as per Investigator's judgement, make the subject ineligible.

### **5.3.3 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
- Ability to perform self-administration of study treatment, availability of caregiver to administer study treatment, or ability to visit study site to administer study treatment
- Concomitant medication restrictions as described in Section 6.13
- Fasting (water and concomitant medications are permitted) for at least 9 hours prior to all study visits

The Investigator (or designee) should review these restrictions with the subject when assessing eligibility 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.

### **5.3.4 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).

Subjects 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 Safety Follow-Up Visit. 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 International 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 International or R-Pharm International's designee in advance whenever possible.

## **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 wellbeing of the subject.

The timing for all study visits during the open-label Treatment Period is relative to OLE Baseline. 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. There is a  $\pm 5$  day visit window for all study visits with the exception of the 3 Safety Follow-Up Visits ( $\pm 7$  days).

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.

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

The standard order should be:

- All PRO questionnaires (prior to any discussion between the subject and study 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 Open-label Treatment Period Visits: Visit 1 (OLE Baseline/Week 24) through Visit 9 (Week 88)**

##### **5.4.1.1 Visit 1 (OLE Baseline/Week 24)**

Written informed consent for the OLE study must be obtained prior to the performance of any protocol-specific procedures at Visit 1 (OLE Baseline/Week 24). 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 attending all scheduled study site visits, including the EoT Visit and Safety Follow-Up Visits, regardless of whether the subject chooses to discontinue from the study treatment, or not. 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 informed consent form (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).

If a subject meets all study eligibility criteria, the Investigator will randomize the subject via the Interactive Web Response System (IWRS) to one of the two open-label treatment groups (see Section 5.2). Subjects will keep the same subject number that they were assigned during the core study.

Visit 1 (OLE Baseline/Week 24) in the OLE study is the same as the Visit 15 (EoT/Week 24) visit in the core CREDO studies. Any assessments specified for the OLE Baseline Visit that duplicate the assessments specified for Week 24 in the core studies should only be performed once.

In addition to obtaining subject informed consent, the following assessments should be performed:

- Check eligibility criteria.
- Randomize subject (Via 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).
- Perform joint counts (Independent Joint Assessment) (see Section 7.1.2).
  - 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 joint count (SJC) and tender joint count (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.
- Assess AEs/SAEs.
- Assess injection site reactions that have occurred since the previous injection (see Section 7.4.3.5).
- Administer Physician Global Assessment (VAS) (see Section 7.1.5).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire (see Section 7.4.9).
- Record height and weight (see Section 7.4.7.3).
- Record vital signs (see Section 7.4.7.2).
  - BP and heart rate also need to be reassessed 1 and 2 hours postdose.
- Perform complete physical examination (see Section 7.4.7.1).
- Perform CV risk assessment (see Section 7.4.7.4).
- Perform 12-lead electrocardiogram (ECG) (see Section 7.4.7.4).
- Perform chest X-ray (see Section 7.4.7.6).
  - Chest X-ray need not be conducted if performed and evaluated within 8 weeks prior to Visit 1 (OLE Baseline/Week 24), and if the films or images are available and included in the subject's source documents.
- Collect samples for international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen (see Section 7.4.6.1).
- Measure ESR (see Section 7.4.6.1).

- Collect sample to measure CRP level (see Section 7.4.6.1).
- Collect samples for lipid panel and CV risk panel (see Section 7.4.6.1).
- Collect samples for chemistry panel, hematology assessments, antinuclear antibodies (ANA), and double-stranded DNA (dsDNA) antibodies (see Section 7.4.6.1).
- Collect PK sample prior to the first dose of study treatment (see Section 7.2).
- Collect sample for analysis of ADAs (see Section 7.3).
- Perform urine pregnancy test for females of childbearing potential only.
- Perform urinalysis (see Section 7.4.6.1).
- Allocate study treatment through the IWRS.
- Distribute Subject Diary and train subjects to properly complete the Subject Diary (see Section 5.5).
- Perform training for study treatment preparation, storage, and administration (see Section 6.8).
- Administer study treatment.
  - Study treatment will be administered by the subject (or caregiver, if applicable) at this visit, and the Investigator must observe this administration to ensure that proper procedures are followed
  - Subcutaneous injections may be rotated among the thighs and abdomen.
  - 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.

#### **5.4.1.2 Visit 2 (Week 26)**

The following assessments will be performed at Visit 2 (Week 26):

- Assess AEs/SAEs 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.
- Record weight.

- Record vital signs.
- Perform partial physical examination (see Section 7.4.7.1).
- Collect samples for chemistry panel and hematology assessments.
- Collect sample for glycosylated hemoglobin (HbA<sub>1c</sub>) assessment (subjects with confirmed diabetes mellitus only).
- Collect and review Subject Diary.
- For OKZ 64 mg q2w treatment group only:
  - Allocate study treatment through the IWRS.
  - Perform training for study treatment preparation, storage, and administration
  - Administer study treatment.
    - Study treatment will be administered by the subject (or caregiver, if applicable) at this visit, and the Investigator must observe this administration to ensure that proper procedures are followed
    - Subjects will remain at the study site for at least 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

#### **5.4.1.3 Visit 3 (Week 28)**

The following assessments will be conducted at Visit 3 (Week 28):

- Assess AEs/SAEs 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.
- Record weight.
- Record vital signs.
- Perform partial physical examination.
- Collect samples for chemistry panel and hematology assessments.
- Perform urine pregnancy test for females of childbearing potential only.

- Collect and review Subject Diary.
- Allocate study treatment through the IWRS.
  - In addition to study treatment for Visit 3 (Week 28) administration, subjects will receive 1 vial or 1 pre-filled syringe (PFS) of OKZ for each dose that is scheduled to be administered prior to Visit 4 (Week 36).
- Perform training for study treatment preparation, storage, and administration (OKZ 64 mg q4w treatment group only).
- Administer study treatment.
  - Study treatment will be administered by the subject (or caregiver, if applicable) at this visit, and the Investigator must observe this administration to ensure that proper procedures are followed (observation is obligatory for OKZ 64 mg q4w treatment group only)
  - Subjects in the OKZ 64 mg q4w treatment group will remain at the study site for at least 30 minutes after the injection to be assessed for onset of any systemic injection reactions.

#### **5.4.1.4 Visit 4 (Week 36)**

Starting at Visit 4 (Week 36) and then at all onsite visits until the end of the open-label Treatment Period, all subjects will be assessed for response to treatment, with nonresponders defined as subjects who do not improve by at least 20% in SJC and TJC (66-68 joint assessment) from the Core Baseline assessment. Investigators will be requested to review carefully the response status at these time points and make appropriate actions based on local guidelines regarding management of the subjects, including possible adjustments in background therapy (see Section 6.13.3) or discontinuation of study treatment (see Section 6.11).

The following assessments will be conducted at Visit 4 (Week 36):

- 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).

- Assess AEs/SAEs 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.
- Record vital signs.
- Perform partial physical examination.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for chemistry panel and hematology assessments.
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.
- Collect and review Subject Diary.
- Assess treatment compliance (see Section 6.7).
  - Subjects who received vials must return all used/unused vials to the study site.
  - Subjects who received PFS must return carton of all used/unused PFS to the study site.
- Allocate study treatment through the IWRS.
  - In addition to study treatment for Visit 4 (Week 36) administration, subjects will receive 1 vial or 1 PFS of OKZ for each dose that is scheduled to be administered prior to Visit 5 (Week 44).
- Administer study treatment.

#### **5.4.1.5 Visit 5 (Week 44)**

The following assessments will be conducted at Visit 5 (Week 44):

- Administer Patient Global Assessment of Disease Activity (VAS).
- Administer Patient Assessment of Pain (VAS).
- Administer HAQ-DI.
- Perform joint counts (Independent Joint Assessment).
- Assess Treatment Response
- Assess AEs/SAEs 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.
- Record vital signs.
- Perform partial physical examination.
- Collect sample to measure CRP level.
- Measure ESR.
- Collect samples for chemistry panel and hematology assessments.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect and review Subject Diary.
- Assess treatment compliance.
- Allocate study treatment through the IWRS.
  - In addition to study treatment for Visit 5 (Week 44) administration, subjects will receive 1 vial or 1 PFS of OKZ for each dose that is scheduled to be administered prior to Visit 6 (Week 52).
- Administer study treatment.



#### **5.4.1.6 Visit 6 (Week 52)**

The following assessments will be conducted at Visit 6 (Week 52):

- 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).
- Assess Treatment Response
- Assess AEs/SAEs 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.
- Record vital signs.
- Perform complete physical examination.
- Perform CV risk assessment.
- Perform 12-lead ECG.
- Perform chest X-ray.
  - Chest X-ray need not be conducted if performed and evaluated within 8 weeks prior to Visit 6 (Week 52), and if the films or images are available and included in the subject's source documents.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for lipid panel.

- Collect samples for chemistry panel, hematology assessments, ANAs, and dsDNA antibodies.
- Collect sample for HbA<sub>1c</sub> assessment (subjects with confirmed diabetes mellitus only).
- Perform IGRA testing only for subjects who had a negative IGRA result at the previous assessments (including Week 22 assessment of the core study) unless another approach is required by local practice. If results are indeterminate, the IGRA can be repeated once.
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.
- Collect and review Subject Diary.
- Assess treatment compliance
- Allocate study treatment through the IWRS.
  - In addition to study treatment for Visit 6 (Week 52) administration, subjects will receive 1 vial or 1 PFS of OKZ for each dose that is scheduled to be administered prior to Visit 7 (Week 64).
- Administer study treatment.

#### **5.4.1.7 Visit 7 (Week 64)**

The following assessments will be conducted at Visit 7 (Week 64):

- 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).
- Assess Treatment Response
- Assess AEs/SAEs 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.
- Record vital signs.
- Perform partial physical examination.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for chemistry panel and hematology assessments.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect and review Subject Diary.
- Assess treatment compliance.
- Allocate study treatment through the IWRS.
  - In addition to study treatment for Visit 7 (Week 64) administration, subjects will receive 1 vial or 1 PFS of OKZ for each dose that is scheduled to be administered prior to Visit 8 (Week 76).
- Administer study treatment.

#### **5.4.1.8 Visit 8 (Week 76)**

The following assessments will be conducted at Visit 8 (Week 76):

- 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).
- Assess Treatment Response

- Assess AEs/SAEs 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.
- Record vital signs.
- Perform partial physical examination.
- Perform CV risk assessment.
- 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.
- Collect samples for chemistry panel and hematology assessments.
- Collect sample for HbA<sub>1c</sub> assessment (subjects with confirmed diabetes mellitus only).
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.
- Collect and review Subject Diary.
- Assess treatment compliance.
- Allocate study treatment through the IWRS.
- In addition to study treatment for Visit 8 (Week 76) administration, subjects will receive 1 vial or 1 PFS of OKZ for each dose that is scheduled to be administered prior to Visit 9 (Week 88).

- Administer study treatment.

#### **5.4.1.9 Visit 9 (Week 88)**

The following assessments will be conducted at Visit 9 (Week 88):

- 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).
- Assess Treatment Response
- Assess AEs/SAEs 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.
- Record vital signs.
- Perform partial physical examination.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for chemistry panel and hematology assessments.
- Perform urine pregnancy test for females of childbearing potential only

- Collect and review Subject Diary.
- Assess treatment compliance.
- Allocate study treatment through the IWRS.
  - In addition to study treatment for Visit 9 (Week 88) administration, subjects will receive 1 vial or 1 PFS of OKZ for each dose that is scheduled to be administered prior to Visit 10 (EoT/Week 106).
- Administer study treatment.

#### **5.4.2 Visit 10/End of Treatment (2 Weeks After the Last Dose of the Study Treatment)/(Week 106)**

Visit 10 (EoT/Week 106) will be performed at Week 106 for subjects who complete all scheduled study visits or 2 weeks after the last dose of study treatment for subjects who discontinue study treatment prematurely.

The following assessments will be performed at Visit 10 (EoT/Week 106) 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).
- Assess Treatment Response
- Administer Physician Global Assessment (VAS).
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire.
- Assess AEs/SAEs (and injection site reactions) that have occurred since the previous visit.
- Record weight.
- Record vital signs.

Perform complete physical examination.

- Perform CV risk assessment.
- Perform 12-lead ECG.
- Perform chest X-ray.
  - Chest X-ray need not be conducted if performed and evaluated within 8 weeks prior to Visit 10 (EoT/Week 106), and if the films or images are available and included in the subject's source documents.
- Collect samples for INR, aPTT, and fibrinogen.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for lipid panel and CV risk panel.
- Collect samples for chemistry panel, hematology assessments, ANAs, and dsDNA antibodies.
- Collect sample for HbA<sub>1c</sub> assessment (subjects with confirmed diabetes mellitus only).
- Perform IGRA testing only for subjects who had a negative IGRA result at the previous assessments (including Week 22 assessment of the core study) unless another approach is required by local practice. If results are indeterminate, the IGRA can be repeated once.
- Collect sample for analysis of ADAs.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.
- Collect and review Subject Diary.
- Assess treatment compliance.
- Change subject status in the IWRS

### **5.4.3 Safety Follow-Up: Visits SFU-1, SFU-2, and SFU-3**

#### **5.4.3.1 Visit SFU-1 (Week 108 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/SAEs.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Record vital signs.
- Perform partial physical examination.
- Measure ESR.
- Collect sample to measure CRP level.
- Collect samples for chemistry panel and hematology assessments.
- Perform urine pregnancy test for females of childbearing potential only.

#### **5.4.3.2 Visit SFU-2 (Week 112 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/SAEs.
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Administer TB risk questionnaire.
- Record weight.
- Record vital signs.
- Perform partial physical examination.
- Measure ESR.
- Collect sample to measure CRP level.



- Collect samples for chemistry panel and hematology assessments.
- Perform urine pregnancy test for females of childbearing potential only.

#### **5.4.3.3 Visit SFU-3 (Week 126 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/SAEs
- Record details of contraceptive history/status.
- Record concomitant medications and concomitant non-drug therapies.
- Record weight.
- Record vital signs.
- Perform complete physical examination.
- Perform 12-lead ECG.
- Collect samples for INR, aPTT, and fibrinogen.
- Collect samples for lipid panel and CV risk panel.
- Collect samples for chemistry panel, hematology assessments, ANAs, and dsDNA antibodies.
- Perform urine pregnancy test for females of childbearing potential only.
- Collect sample for urinalysis.

#### **5.4.4 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.

R-Pharm International's designee should be informed of these incidents in a timely fashion.

### **5.5 Subject Diary**

At Visit 1 (OLE Baseline/Week 24), a Subject Diary will be distributed to all subjects and subjects will be trained to properly complete the Subject Diary.

At Visit 1 (OLE Baseline/Week 24) and at each scheduled visit during the open-label Treatment Period (Visits 2 [Week 26] through 9 [Week 88]), the Investigator will provide the subject with preprinted dates for each dose of study treatment that will be administered prior to the next scheduled visit. Visit 2 date and further CREDO 4 visit dates should be calculated from the actual CREDO 4 Randomization date. Following each administration of study treatment, the subject will record the actual date, time, and location of study treatment administration in the Subject Diary; the identity of the person who administered the study treatment; any problems that occur during the injection; and any complaints, signs, or symptoms that occur during or after the injection.

The Subject Diary will instruct subjects to contact the Investigator if they experience any problems with the injection or if they experience any significant signs or symptoms during or after the injection.

The Investigator will collect completed pages of the Subject Diary at Visits 2 (Week 26) through 10 (EoT/Week 106). Completed pages of the Subject Diary will serve as source documents, and the Investigator will transfer the data, including the date, time, and location of each SC injection; the identity of the person who administered the study treatment; and any departures from the intended regimen from the Subject Diary into the appropriate page(s) of the eCRF. The Investigator will also review any complaints, signs, or symptoms recorded in the Subject Diary and record any AEs in the eCRF, as appropriate.

The Subject Diary will not be used during the Safety Follow-Up Period.

## **6. STUDY TREATMENTS**

### **6.1 Study Treatment Administered**

#### **Study Treatment**

All eligible subjects will be randomized to 1 of the 2 OKZ treatment groups as described in Sections 5.2 and 6.5. A detailed description of the study treatment (OKZ) is provided in Section 6.2.

#### **Background Therapy**

As per inclusion criterion No. 3 (see Section 5.3.1), subjects must have been treated with MTX at a dose of 15 to 25 mg/week (or  $\geq 10$  mg/week if there is documented intolerance to higher doses) during the core study with a stable dose and mode of administration (oral, SC, or IM). For the first 12 weeks of the OLE study (i.e., through Week 36), the dose of MTX should remain unchanged and may be adjusted only for safety reasons according to Investigator discretion (see guidelines in Appendix 1 [see Section 13.1]). After Visit 4 (Week 36), the Investigator may adjust the MTX dosage and route, per local guidelines.

Subjects who were prescribed rescue medication(s) (sulfasalazine and/or hydroxychloroquine) during the core studies will be asked to continue these medications at the same dose for the first 12 weeks of the OLE study (i.e., through Visit 4 [Week 36]). After Visit 4 (Week 36), the Investigator may adjust these background medications if deemed appropriate.

Additional details regarding background therapy, including adjustments to background therapy that are permitted after Visit 4 (Week 36), are provided in Section 6.13.3.

### **6.2 Identity of Study Treatment**

Olokizumab will be supplied by R-Pharm International 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. The OKZ drug substance is the fully formulated product, which is sterilized by filtration and aseptically filled in vials or syringes to obtain the drug product.

Olokizumab is presented as a sterile solution for SC injection in the following formats:

- A 2 mL clear Type I glass vial with target volume of 0.4 mL. The vial is closed with a chlorobutyl stopper and sealed with an aluminum seal with a polypropylene flip-off cap.
- The PFS is composed of a 1 mL clear Type I glass barrel vial with target volume of 0.4 mL.

The components and composition of the OKZ drug product are presented in Table 2.

**Table 2 Components and Composition of OKZ (CDP6038; L04041) Drug Product**

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

Abbreviations: OKZ = Olokizumab; qs = quantum satis (sufficient quantity).

a. Added during the drug substance manufacturing process.

### 6.3 Packaging and Labeling

Study treatment will be supplied in cartons containing 1 vial or 1 PFS of OKZ. 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 at the study site.

Olokizumab will be shipped refrigerated at +2°C to +8°C (36°F to 46°F). Olokizumab should be stored at +2°C to +8°C (36°F to 46°F) in a secure, temperature-controlled refrigerator. Olokizumab will be supplied centrally. Please refer to the Pharmacy Manual for additional details on storage requirements.

With study treatment that is dispensed to subjects for administration of OKZ at home, subjects will receive a Subject Leaflet containing details of the correct storage and transportation of study treatment.

## **6.5 Method of Assigning Subjects to Treatment Group**

Subjects will be randomized using the IWRS (an automated web randomization system) to 1 of 2 treatment groups (OKZ 64 mg q2w or OKZ 64 mg q4w). The IWRS will allocate the treatment group and assign the study treatment based on the treatment a subject received in the core studies. Subjects who received OKZ in the core study in which they participated (including subjects who received placebo in Study CL04041025 and were re-randomized to OKZ at Week 16) will receive the same OKZ treatment regimen in the OLE study (OKZ 64 mg q2w or OKZ 64 mg q4w). Subjects who received placebo (Study CL04041022 and Study CL04041023) or adalimumab (Study CL04041023) in the core study in which they participated will be randomized in a 1:1 ratio to receive OKZ 64 mg q2w or OKZ 64mg q4w in the OLE study.

The IWRS system will also manage study site drug supply and subject drug dispensation. Study staff will request study treatment assignments via the 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 pharmacist (or delegate) at the study site is responsible for maintaining an adequate record of study treatment that is received, distributed, and returned by subjects to the study site at each scheduled visit (all used/unused vials, unused PFS, and/or used PFS cartons). The study treatment accountability records must be kept current, available for monitoring by the study monitor, and available for inspection at any time. Study treatment materials at the study site should be kept in a secured location.

Used study treatment must be discarded as a biohazard, and the handling, disposal, and destruction details will be detailed within the Pharmacy Manual.

The Investigator is responsible for maintaining an adequate record of study treatment administration (see Section 6.8) and study treatment compliance (see Section 6.7).

Detailed instructions on drug accountability are provided within 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 data. The prescribed dosage, timing, and mode of administration may not be changed.

A monitor will review the pharmacy records at each study site including the drug dispensing records. The pharmacist (or designee) should record all study treatment dispensed to subjects

and all used/unused vials, unused PFS, and/or used PFS cartons returned by subjects to the study site. The monitor will verify the dispensing records against vials/PFS cartons to ensure 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 staff to ensure that the errors are not repeated. 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's review.

Subjects will record details of study treatment administration in the Subject Diary (see Section 5.5). Subjects will be required to return all used/unused vials and/or used PFS cartons to the study site at each scheduled visit. Subject compliance with the study treatment will be assessed by study site staff at each visit during the Treatment Period, with compliance defined as the administration of the study treatment conforming to 80% to 100% of the plan, in accordance with the requirements specified in the Protocol dosing of investigational drug, in addition to the following:

- For subjects in the OKZ 64 mg q2w treatment group, no more than 2 consecutive missed injections during the Treatment Period.
- For subjects in the OKZ 64 mg q4w treatment group, no consecutive missed injections during the Treatment Period.

Any subject who deviates from the dosing schedule or misses any scheduled study treatment should be reported to R-Pharm International and/or R-Pharm International's designee promptly.

## **6.8 Preparation and Administration of Study Treatment**

Each subject will be provided with the following materials as applicable:

- Study treatment will be administered in one of the following forms (as described in Section 6.2.1):
  - Olokizumab vials and sterile disposable syringes and needles for SC injection, OR
  - Olokizumab PFS.
- A container for disposal of biomedical waste (i.e., used PFS/syringes/needles).
- Cooler bag for OKZ transportation.

Subjects will receive a Subject Leaflet containing instructions on study treatment preparation, administration, storage, transportation, and disposal and return of used/unused

vials/PFS/syringes/needles to the study site. The Subject Leaflet will instruct the subject to contact the Investigator in the event that difficulties arise with the administration of study treatment. The Subject Leaflet will also contain detailed instructions regarding what to do if there is a problem with a vial or PFS.

The number of PFS or vials, syringes, and needles received by the subject at each visit will depend upon the treatment group to which the subject is assigned; the subject will receive 1 PFS or 1 vial with sterile disposable syringe and needle for SC injection of study treatment that is scheduled to occur prior to the next scheduled visit. Subjects will be instructed that a new PFS or vial, syringe, and needle for SC injection should be used for each administration of study treatment, and that the PFS or vials, syringes, or needles should not be re-used.

Subjects will be instructed to return used/unused study medication as follow:

- For subjects who receive vials, all used/unused vials (if any) must be returned to the study site at the next scheduled visit. Subjects will be instructed that all used syringes and needles should be disposed of in the supplied container for disposal of biomedical waste.
- For subjects who receive PFS, empty PFS cartons and unused PFS (if any) should be returned to the study site at the next scheduled visit. Subjects will be instructed that all used PFS should be disposed of in the supplied container for disposal of biomedical waste.

Subjects who receive vials/needles/syringes will be advised that the syringes should be prepared in a way timed to avoid exceeding the stipulated stability time of the prepared product, and the solution may remain in the syringe for a maximum of 4 hours prior to its administration.

Both the PFS and prepared syringes should be warmed at room temperature prior to study treatment administration.

Subcutaneous injections of OKZ 64 mg will be administered by the subject (or caregiver, if applicable) q2w or q4w throughout the open-label Treatment Period. Administration of study treatment by a caregiver (i.e., relative or other free-of-charge person) should be limited and only take place if the subject encounters difficulties with the injection or if the subject is unable to self-administer the study treatment.

Study site staff will train all study subjects on the self-administration of OKZ during their first 2 study visits (Visit 1 [Week 24] and Visit 2 [Week 26] for subjects receiving OKZ 64 mg q2w, and Visit 1 [Week 24] and Visit 3 [Week 28] for subjects receiving OKZ 64 mg q4w). For study subjects who have a caregiver who has consented to study

participation, that caregiver should be present during the above mentioned visits, and trained by site staff, to administer the OKZ to the subject. If the subject has a caregiver who is not present at one or both training visits, the site staff can provide training at a later study visit.

Injections of study treatment administered by the subject or caregiver (if applicable) must be observed by study site staff during the first 2 scheduled administrations (Visit 1 [Week 24] and Visit 2 [Week 26] for subjects receiving OKZ 64 mg q2w, and Visit 1 [Week 24] and Visit 3 [Week 28] for subjects receiving OKZ 64 mg q4w) to ensure that proper procedures are followed. This training may be repeated at any visit to the study site if requested by the subject (or caregiver, if applicable), or if deemed appropriate by the Investigator. In the event that a subject is unable to self-administer study treatment and a caregiver is not available, the subject may visit the study site to receive a scheduled injection. Subjects will record details of study treatment administration in the Subject Diary as detailed in Section 5.5.

If desired, the subject may rotate SC injections among the thighs and abdomen. All subjects will remain at the study site for at least 2 hours after the first administration of study treatment (Visit 1 [OLE Baseline/Week 24]), and for at least 30 minutes after the second administration of study treatment (Visit 2 [Week 26] for subjects receiving OKZ 64 mg q2w and Visit 3 [Week 28] for subjects receiving OKZ 64 mg q4w) to be assessed for the onset of any systemic injection reactions as described in Section 7.4.3.2. For injections administered by the subject (or caregiver, if applicable), subjects will record in the Subject Diary (see Section 5.5) any complaints, signs, or symptoms that occur during or after the injection.

In all cases, there must be at least 1 week between all doses of study treatment.

If a subject misses a scheduled dose, study treatment should be administered as soon as possible, while ensuring that there will be at least 1 week between the current injection and the next scheduled injection. If the remaining interval between the current dose and the next scheduled dose appears to be less than 1 week, then the current dose should be skipped. If the subject is unable to administer study treatment in the allowed window, or if the subject is aware in advance that they will miss a scheduled dose (e.g., due to travel, etc), the subject should contact the Investigator for guidance. The Investigator can contact the Medical Monitor for discussion on a case-by-case basis.

In the case of an AE that requires interruption of study treatment administration, as assessed clinically by the Investigator or as required by the protocol (see Appendix 1 [Section 13.1]), study treatment administration can be delayed, while ensuring that there will be at least 1 week between the current dose and the next scheduled dose. If the subject cannot be dosed within the allowed window due to lack of resolution of the AE, then the current dose should be skipped. Study treatment administration should resume at the next scheduled dosing date



when interruption of study treatment administration is no longer required, based on resolution of the AE and Investigator judgement.

Detailed instructions for the Investigator on study treatment preparation, handling, and administration 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 are not allowed in this study.

Dose adjustments for OKZ are not allowed in this study. For guidelines regarding dose adjustments of MTX and any cDMARDs prescribed as rescue medication during the core studies, refer to Section 6.1.

## **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, the subject should be encouraged to return for the EoT and Safety Follow-Up Visits (as detailed in Sections 5.4.2 and 5.4.3). All Safety Follow-Up assessments should be performed unless the subject also withdraws informed consent to participate in the study (see Section 5.3.4). If a subject that discontinues study treatment does not return for the scheduled EoT or Safety Follow-Up Visits, 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**

Temporary discontinuation of study treatment is required for the situations described below. The Investigator should contact the Medical Monitor for guidance regarding restarting study treatment.

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 remains  $>3 \times$  ULN with total bilirubin  $\leq 2 \times$  ULN after repeat laboratory testing.
- Subjects have an active or clinically significant infection.
- Subject has a suspected malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin), after confirmation with the Medical Monitor.

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 [Section 7.4.6.2], 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).

### **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 International or R-Pharm International's designee must be informed immediately, and the subject may be discontinued from 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, R-Pharm International or R-Pharm International's designee must be informed as soon as it can be possible, and the case will be reviewed by R-Pharm International on a case-by-case basis and the noncompliant subject can be discontinued from the 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 discontinued in the following circumstances:

- Investigator decides that the subject should be discontinued from the 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 International or R-Pharm International'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 1 [Section 13.1]):
  - ALT or AST elevations  $>8 \times$  ULN at any time, regardless of total bilirubin or accompanying symptoms
  - ALT or AST  $>5 \times$  ULN for  $\geq 2$  weeks regardless of total bilirubin or accompanying symptoms. The elevation should be continuous for  $\geq 2$  consecutive weeks. If the level decreases for some time within 2 weeks, subject permanent discontinuation is not mandated, but left under Investigator discretion. Resuming the IMP should be discussed on a case by case basis.
  - ALT or AST elevations  $>3 \times$  ULN and total bilirubin value  $>2 \times$  ULN at any time
  - AST or ALT elevations  $>3 \times$  ULN accompanied by symptoms which, as determined by the Investigator, are the result of hepatic injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, eosinophilia [ $>5\%$ ])
- Subject presents with any of the following laboratory abnormalities:
  - Absolute neutrophil count  $<500 \times 10^6/L$  ( $<500/mm^3$ )
  - Two sequential lymphocyte counts  $<500 \times 10^6/L$  ( $<500/mm^3$ )
  - Platelet count  $<50 \times 10^9/L$  ( $<50,000/mm^3$  or  $<50,000 \times 10^6/L$ )
  - Two sequential hemoglobin values  $\leq 8.0$  g/dL and decreased  $\geq 20$  g/L (2 g/dL) below OLE Baseline
  - Creatinine value  $>2 \times$  ULN
- Subject has confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
- R-Pharm International, a regulatory agency, or an ethical committee stops the study for any reason.
- Subject has a GI perforation.

- Subject diagnosed with diverticulitis
- Subject has a confirmed active TB.
- Subject has a positive IGRA result or repeated indeterminate IGRA results during the study, unless active TB is ruled out and the Medical Monitor confirms that study treatment can be resumed as described below:
  - Subjects may resume the administration of study treatment if active TB is ruled out by a certified TB specialist or pulmonologist who is familiar with treating TB (as acceptable per local practice). The subject must also start prophylactic LTBI therapy according to country-specific/CDC guidelines (see Appendix 4 [Section 13.4]) and agree to complete the entire course of recommended LTBI therapy. Study treatment should not be administered until active TB is ruled out and the subject starts LTBI therapy.
- Subject has a severe or life-threatening infection that requires hospitalization.
- Subject has a malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin), after confirmation with the Medical Monitor.

## 6.12 Blinding

This is an open-label study. The subjects, Investigators, study site staff, and Sponsor will not be blinded.

An independent CVAC and DSMB will be established for this study to assess safety on an ongoing basis (see Section 7.4.4). Members of the CVAC will be blinded to treatment group. Members of the DSMB will be partially blinded to treatment group: they will be aware of which subjects are in the same treatment group, but they will not be aware of the treatment assigned to each group. However, members of the DSMB may be unblinded in the event that safety monitoring identifies an issue that needs to be addressed at the treatment group level (see Section 7.4.8).

## 6.13 Prior and Concomitant Treatments

For the first 12 weeks of the OLE study (i.e., through Visit 4 [Week 36]), background therapy requirements (ie, concomitant treatment with MTX and with permitted rescue medication(s) prescribed in the core studies) are detailed in Section 6.1.

Concomitant treatment with folic acid  $\geq 5$  mg per week or equivalent is required for all subjects.

Other specifically allowed medications are discussed in Section 6.13.2.

Specific treatments prohibited during the course of the study are described in Table 3. Other medications and non-drug therapies not listed within Table 3 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. 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 3 Prohibited Medications**

Treatment	Restriction
cDMARDs other than MTX	<ul style="list-style-type: none"> <li>Treatment with cDMARDs other than MTX, including leflunomide, is prohibited during the entire study, with the exception of sulfasalazine and/or hydroxychloroquine if they were assigned as rescue medication during the core study. <ul style="list-style-type: none"> <li>During the first 12 weeks of the OLE study (i.e., up to Visit 4 [Week 36]), cDMARD background therapy (MTX for all subjects; sulfasalazine and/or hydroxychloroquine for subjects assigned rescue medication in the core studies) should remain unchanged and may be adjusted only for safety reasons according to Investigator discretion. Subjects from CL04041025 are exempt from this restriction.</li> <li>After the first 12 weeks of the OLE study (i.e., after Visit 4 [Week 36]), dose modifications of a subject's existing background cDMARD therapy are permitted, if deemed appropriate by the Investigator, per local guidelines (see Section 6.13.3). Subjects that did not receive sulfasalazine and/or hydroxychloroquine in the core studies should not be assigned these medications in the OLE study.</li> </ul> </li> </ul>
bDMARDs/kinase inhibitors	<ul style="list-style-type: none"> <li>Treatment with bDMARDs or kinase inhibitors is prohibited during the entire study.</li> </ul>
Corticosteroids	<ul style="list-style-type: none"> <li>During the first 12 weeks of the OLE study (i.e., up to Visit 4 [Week 36]): <ul style="list-style-type: none"> <li>The use of parenteral corticosteroids (with the exception of IA corticosteroids) is prohibited.</li> <li>The use of oral corticosteroids &gt;10 mg/day prednisone or equivalent is prohibited. <b>Dose tapering is permitted according to Investigator discretion; other changes in dose are prohibited unless the Investigator changes the dose for safety reasons.</b></li> </ul> </li> <li>After the first 12 weeks of the OLE study (i.e., after Visit 4 [Week 36]), a change in the route of administration of corticosteroids or a dose adjustment of oral corticosteroids is permitted, including transient dose increases with dose tapering as soon as possible after the dose increase (see Section 6.13.3), per Investigator discretion and local practice.</li> </ul>

Treatment	Restriction
NSAIDs	<ul style="list-style-type: none"> <li>Initiation of new NSAIDs is prohibited during the first 12 weeks of the OLE study.               <ul style="list-style-type: none"> <li>Stable doses of NSAIDs are permitted during the first 12 weeks of the OLE study if the subject received these NSAIDs during the core study (see Section 6.13.2). <b>Dose tapering is permitted according to Investigator discretion</b>; other changes in dose are prohibited 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).</li> </ul> </li> <li>After the first 12 weeks of the OLE study (i.e., after Visit 4 [Week 36]), dose modification and switching of NSAIDs is permitted (see Section 6.13.3), per Investigator discretion and local guidelines.</li> <li>Aspirin use at daily doses up to 325 mg is permitted throughout the study if indicated for CV protection. At this dose, aspirin will not be considered an NSAID.</li> </ul>
Analgesics	<ul style="list-style-type: none"> <li>Analgesics, including opioids, are prohibited during the first 12 weeks of the OLE study with the following exception (see Section 6.13.2):               <ul style="list-style-type: none"> <li>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 OLE Baseline assessment.</li> </ul> </li> <li>After the first 12 weeks of the OLE study (i.e., after Visit 4 [Week 36]), analgesics and opioids are permitted.</li> </ul>
Hyaluronic acid	<ul style="list-style-type: none"> <li>Intra-articular hyaluronic acid is prohibited during the first 12 weeks of the OLE study.</li> <li>After the first 12 weeks of the OLE study (i.e., after Visit 4 [Week 36]), IA hyaluronic acid is permitted.               <ul style="list-style-type: none"> <li>Joints that receive IA hyaluronic acid should be omitted from all subsequent joint assessments (Sections 7.1.2, 7.1.6, and 7.1.7) and should be rated with their pre-injection status for the remainder of the study.</li> </ul> </li> </ul>
Vaccination	<ul style="list-style-type: none"> <li>Live and live attenuated vaccines are prohibited during the entire study.</li> </ul>

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; CV = cardiovascular; IA = intra-articular; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; OLE = open-label extension.

### 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  $\leq 10$  mg/day of prednisone or equivalent are permitted during the first 12 weeks of the OLE study, with dose tapering permitted according to Investigator discretion. Other dose adjustments are not permitted during the first 12 weeks of the OLE study unless the Investigator changes the dose for safety reasons.
  - Dose modification is permitted after Visit 4 (Week 36) (see Section 6.13.3), per the Investigator's discretion and local practice, including transient dose increases with dose tapering as soon as possible after the dose increase.
  - Investigator should take into consideration the AEs associated with the continuous use of corticosteroids (e.g., diabetes mellitus, infections, GI perforations)
- IM or IV corticosteroids
  - Permitted after Visit 4 (Week 36) (see Section 6.13.3)
- Intra-articular (IA) corticosteroids
  - Permitted in a maximum of 3 joints within the study period, not to exceed one injection every 6 months. The cumulative dose for the 3 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).
- Intra-articular hyaluronic acid
  - Permitted after Visit 4 (Week 36). Joints treated with IA hyaluronic acid 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
  - Stable doses of NSAIDs are permitted during the first 12 weeks of the OLE study if the subject received these NSAIDs during the core study, **with dose tapering permitted according to Investigator discretion**. Other dose adjustments are not permitted during the first 12 weeks of the OLE study unless the Investigator changes the dose for safety reasons. Switching of NSAIDs is not allowed prior to Visit 4 (Week 36) of the OLE study. 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).
  - Dose modification and switching of NSAIDs are permitted after Visit 4 (Week 36) (see Section 6.13.3).
- Analgesics
  - Prior to Visit 4 (Week 36), subjects may be treated with paracetamol/acetaminophen 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 OLE Baseline assessment.
  - After Visit 4 (Week 36), analgesics (including opioids) are permitted.
- Inactivated vaccines can be administered in accordance with the standard of care.
  - The effect of OKZ on vaccine response, including inactivated vaccines, is unknown.

### 6.13.3 Modification of Background Therapy

During the first 12 weeks of the OLE study, background MTX (all subjects) and sulfasalazine and/or hydroxychloroquine (for subjects assigned rescue medication starting at Week 14 in the core studies) should remain unchanged and may be adjusted only for safety reasons according to Investigator discretion (see Appendix 1 [Section 13.1] for guidelines on MTX dose reduction). Subjects from CL04041025 are exempt from this restriction, and have their background therapy may be adjusted at the Investigator's discretion.

For subjects who receive background sulfasalazine and/or hydroxychloroquine, periodic safety evaluations for toxicity resulting from sulfasalazine and/or hydroxychloroquine should be undertaken as per the drug label and local guidelines. The maximum allowed doses of sulfasalazine and hydroxychloroquine are:

- Sulfasalazine: 3 g per day



- Hydroxychloroquine: 400 mg per day

Dose tapering of background oral corticosteroids and NSAIDs (if applicable) is permitted according to Investigator discretion, but the dose should otherwise remain unchanged unless the Investigator changes the dose for safety reasons.

After the first 12 weeks of the OLE study (i.e., after Visit 4 [Week 36]), the Investigator may modify background therapy, if deemed appropriate, per local guidelines. Modifications to background therapy may include:

- Modification of MTX for all subjects
- Modification of sulfasalazine and/or hydroxychloroquine for subjects assigned rescue medication starting at Week 14 in the core studies
  - Sulfasalazine and/or hydroxychloroquine may not be prescribed to subjects who did not receive these rescue medications in the core studies.
- Modification of oral corticosteroids (including initiation of doses  $\leq 10$  mg/day of prednisone or equivalent)
- Administration of IM or IV corticosteroids
- Modification of NSAIDs (including switching of NSAIDs)

#### **6.14 Medical Treatment for Subjects after End of Treatment Period**

After completion of the 82-week, open-label Treatment Period, or after premature discontinuation of study treatment, subjects will enter the Safety Follow-Up Period. 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. The calculations are based on a  $\geq 20\%$ ,  $\geq 50\%$ , and  $\geq 70\%$  improvement from baseline in the SJC assessed in 66 joints and in the TJC assessed in 68 joints; and a  $\geq 20\%$ ,  $\geq 50\%$ , and  $\geq 70\%$  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, 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 as in the core studies 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 IA corticosteroids or IA hyaluronic acid (see Section 6.13.2), 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 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 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:

$$\text{DAS28 (CRP)} = 0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.36 \times \log_{\text{nat}} (\text{CRP} + 1) + 0.014 \times \text{Patient Global Assessment of Disease activity (VAS)} + 0.96$$

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 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:

$$\text{DAS28 (ESR)} = 0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.70 \times \log_{\text{nat}}(\text{ESR}) + 0.014 \times \text{Patient Global Assessment of Disease Activity (VAS)}$$

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:

$$\text{SDAI} = \text{SJC} + \text{TJC} + \text{Patient Global Assessment of Disease Activity (VAS)} + \text{Physician Global Assessment (VAS)} + \text{CRP}$$

#### **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:

$$\text{CDAI} = \text{SJC} + \text{TJC} + \text{Patient Global Assessment of Disease Activity (VAS)} + \text{Physician Global Assessment (VAS)}$$

#### **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 Questionnaire – 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, including both 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 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 a 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**

There will be no collection of blood samples for the determination of OKZ concentration in plasma in this study.

- The Week 24 sample is the last sample to be collected in the core studies. This sample must be collected prior to administration of OKZ in the OLE study, and the sample will be analyzed and included in the data set of the core study in which the subject participated, according to the procedures detailed in the core study protocol. This sample will not be analyzed as part of the OLE data set.

To provide documentation that the Week 24 PK sample was collected prior to the first dose of study treatment in this study, the date and time of OKZ administration at Week 24 will be captured in each subject's eCRF.

Although there will be no collection of blood samples in this study for the determination of OKZ concentration in plasma, blood samples that are collected for immunogenicity analysis (see Section 7.3) may also be used to determine OKZ concentrations in plasma if it is

determined that such evaluation may provide additional information regarding subject safety and efficacy of OKZ (e.g., due to unexpected immunogenicity results).

### **7.3 Immunogenicity**

Immunogenicity will be assessed by evaluating the impact of ADAs on subject safety and efficacy 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.

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 International or R-Pharm International'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.

### **7.4 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 7.4.2.3, 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. The Investigator will also collect completed pages of the Subject Diary (see Section 5.5) at Visits 2 (Week 26) through 10 (EoT/Week 106), and the Investigator will review any complaints, signs, or symptoms experienced by the subject in association with administration of study treatment. Completed pages of the Subject Diary will serve as source documents, and information will be recorded on the appropriate pages of the eCRF. The Subject Diary will not be used during the Safety Follow-Up Period. Further routine medical assessments in addition to those specified in Table 1 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.

#### **7.4.1 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 starting at Visit 1 (OLE Baseline/Week 24). 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.

### Severity

The severity of AEs will be characterized according to the CTCAE grades and definitions summarized in Table 4.

**Table 4 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.

#### **7.4.1.1 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?”

#### **7.4.2 Serious Adverse Events**

An SAE experience or reaction is any untoward medical occurrence (whether considered to be related to the 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  $>3 \times$  ULN and total bilirubin  $>2 \times$  ULN
- ALT  $>8 \times$  ULN at any time, regardless of total bilirubin or accompanying symptoms
- ALT  $>5 \times$  ULN for  $\geq 2$  weeks, regardless of total bilirubin or accompanying symptoms. The elevation should be continuous for  $\geq 2$  consecutive weeks. If the level decreases for some time within 2 weeks, subject permanent discontinuation is not mandated, but left under Investigator discretion. Resuming the IMP should be discussed on a case by case basis.
- ALT  $>3 \times$  ULN, accompanied by symptoms which, as determined by the Investigator, are the result of hepatic injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, eosinophilia [ $>5\%$ ]).

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 any of the following criteria are met:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition or
  - Elective or preplanned 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 an 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 International'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 International or their'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 be used, for example, in case of presence of such cardiovascular diagnosis in the source documents or occurrence of an unexpected cardiac death within scenarios as described in Potential MACE Reporting Site Manual. 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 the 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.

#### **7.4.2.1     *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.

#### **7.4.2.2     *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.

#### **7.4.2.3      *Reporting and Follow-up Requirements for Pregnancies***

##### **Pregnancies in Female Subjects**

A urine pregnancy test will be conducted on all females of childbearing potential as presented in the Schedule of Events (Table 1).

If a subject becomes pregnant after the administration of any study treatment, R-Pharm International and/or R-Pharm International'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 cooperation with the treating physician and/or obstetrician.

### **7.4.3 Adverse Events of Special Interest**

The following safety concerns were identified as AESIs based upon either the safety data available to date (refer to the most recent version of the Investigator's Brochure) for OKZ 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 3 (Section 13.3) 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 7.4.3.4).
- 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.

#### **7.4.3.1 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.

#### **7.4.3.2 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 for at least 2 hours after the first administration of study treatment (Visit 1 [OLE Baseline/Week 24]) and for at least 30



minutes after the second administration of study treatment (Visit 2 [Week 26] for subjects receiving OKZ 64 mg q2w and Visit 3 [Week 28] for subjects receiving OKZ 64 mg q4w). For injections administered by the subject (or caregiver, if applicable), subjects will record in the Subject Diary (see Section 5.5) any complaints, signs, or symptoms that occur during or after the injection. Subjects will be asked to contact the Investigator if any significant 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 3 (Section 13.3).**

**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.

#### **7.4.3.3     *Gastrointestinal 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 OKZ is required for subjects who develop diverticulitis and/or GI perforation.

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

#### **7.4.3.4 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  $>3\times$  to  $\leq 5\times$  ULN
- ALT  $>5\times$  ULN
- ALT  $>3\times$  ULN and total bilirubin  $>2\times$  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, gamma-glutamyl transferase (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  $>3\times$  ULN and total bilirubin  $>2\times$  ULN
- ALT  $>8\times$  ULN at any time, regardless of total bilirubin or accompanying symptoms
- ALT  $>5\times$  ULN for  $\geq 2$  weeks, regardless of total bilirubin or accompanying symptoms. The elevation should be continuous for  $\geq 2$  consecutive weeks. If the level decreases for some time within 2 weeks, subject permanent discontinuation is not mandated, but

left under Investigator discretion. Resuming the IMP should be discussed on a case by case basis.

- ALT  $>3 \times$  ULN, accompanied by symptoms which, as determined by the Investigator, are with the result of hepatic injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, eosinophilia [ $>5\%$ ])

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.

#### **7.4.3.5    *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. At all specified visits (see Table 1), the assessment of injection site reactions that have occurred since the previous visit will be made by the Investigator prior to any administration of study treatment. Injection site reactions noticed after on-site study treatment administration, when the subject is still on site or already at home and recorded

them in their diary, will be also reported. All local reactions that are observed will be monitored until they resolve.

#### **7.4.4 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 International based on their expertise. Committee members will not be Investigators in the study, nor will they have any conflict of interest with R-Pharm International 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.

##### **7.4.4.1 Data Safety Monitoring Board**

The independent DSMB members will perform ongoing safety surveillance and provide recommendations to R-Pharm International regarding study conduct. These recommendations will be based mainly on the review of data for AEs and laboratory parameters. Members of the DSMB will be partially blinded: they will be aware of which subjects are in the same treatment group, but they will not be aware of the treatment assigned to each group. Members of the DSMB can request full unblinding of safety data if they consider it necessary.

##### **7.4.4.2 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):

- 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

#### **7.4.5 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. Ongoing AEs (i.e., AEs that started during the core study) should be recorded as an AE in the OLE study only if the frequency, severity, or character of the condition worsens during the OLE 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 International’s designee.

Investigators will seek information on AEs at each subject contact. The Investigator will also review the Subject Diary (Visits 2 [Week 26] through 10 [EoT/Week 106] only), where the subject will record any complaints, signs, or symptoms related to administration of the study treatment. All AEs, whether reported by the subject or noted by study site staff, will be recorded in the subject’s medical record and on the AEs eCRF page.

All AEs that occur at or after Visit 1 (OLE Baseline/Week 24), 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 International’s designee their assessment of the potential relatedness of each AE to protocol procedure and/or study treatment via the eCRF.

Study site staff 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 International’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 date and time to onset, duration, severity, seriousness, and potential relatedness to the study treatment and/or study procedure (i.e., any procedure required by the study protocol). The action taken and the outcome must also be recorded in the AE page of the eCRF.

#### **7.4.5.1 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.

Information contained within the subject diary (see Section 5.5) will not be considered PRO data.

#### **7.4.5.2 Reporting of Serious Adverse Events**

All SAEs that occur at or after Visit 1 (OLE Baseline/Week 24), regardless of the Investigator's assessment on causality, must be recorded on the relevant pages of the eCRF and reported to R-Pharm International 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 as detailed in Section 7.4.5.5, and the timelines and procedure for follow-up reports are the same as those for the initial report. R-Pharm International's designee is responsible for managing the safety database.

R-Pharm International 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 International'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 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.

#### ***7.4.5.3 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators***

R-Pharm International'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 International'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 International'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.

#### ***7.4.5.4 Follow-up of Adverse Events***

Any AEs that occur at or after Visit 1 (OLE Baseline/Week 24) 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. The Investigator should follow each SAE until the event is resolved or returned to the baseline, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. For AEs with a causal relationship to the study treatment, R-Pharm International or its designee must concur with the Investigator's assessment.

For SAEs, nonserious AESIs, and pregnancies, R-Pharm International'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.

#### **7.4.5.5      *Follow-up of Serious Adverse Events by the Investigator***

Any SAEs that occur at or after Visit 1 (OLE Baseline/Week 24) 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.

#### **7.4.6          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 may be performed at the discretion of the Investigator to ensure that the safety of subjects is protected.

##### **7.4.6.1      *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.

- CRP



- ESR: Blood for ESR will be obtained at scheduled visits and tested locally.
- 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, chloride, total protein, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, and albumin
- HbA<sub>1c</sub> is required only for subjects with a confirmed diagnosis of diabetes mellitus.
- Urinary pregnancy testing (human chorionic gonadotropin) is required only for women who are of childbearing potential. Urinary pregnancy testing will be conducted locally using dipsticks provided by the central laboratory. Pregnancy testing may be repeated more frequently than specified in Table 1 (i.e., between study visits) if required by local practices, IRB/IECs or local regulations, or as deemed necessary by Investigator. If more frequent testing is required, the study site will provide the patient with further guidance and testing kit.
- Urinalysis: Specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase
- 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
- IGRA
  - All subjects who had a negative IGRA result at Screening of the core study will have an IGRA performed at Week 22 of the core study (2 weeks prior to OLE Baseline), and the result is to be known prior to OLE Baseline to determine the subject's eligibility for the OLE study (see exclusion criterion No. 3 in Section 5.3.2).
  - For all post-OLE Baseline visits where IGRA is scheduled, the test will be performed only for subjects who had a negative IGRA result at the previous assessments (including Week 22 assessment of the core study) unless another approach is required by local practice. If results are indeterminate, the IGRA can be repeated once.
  - 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.

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.

#### **7.4.6.2     *Mandatory Retesting of Laboratory Abnormalities***

The following laboratory abnormalities require prompt retesting after the initial abnormal result is reported to the study site (within 72 hours of receiving abnormal LFT results and within 5 days of receiving all other abnormal results):

- Any single ALT and/or AST elevation  $>3 \times \text{ULN}$ , regardless of total bilirubin (repeat laboratory testing must include total bilirubin, direct and indirect bilirubin, GGT, INR, alkaline phosphatase, creatine phosphokinase, and hematology assessment)
- Neutrophil count  $<1000 \times 10^6/\text{L}$  ( $<1000/\text{mm}^3$ )
- Lymphocyte count  $<500 \times 10^6/\text{L}$  ( $<500/\text{mm}^3$ )
- Platelet count  $<100,000$  platelets/ $\text{mm}^3$
- Any single hemoglobin value  $<8.0$  g/dL or one that drops  $\geq 20$  g/L (2 g/dL) below OLE Baseline

Clinically significant laboratory abnormalities should be re-tested and followed until resolution, stabilization, or return to baseline values and information will be recorded on the appropriate pages of the eCRF.

#### **7.4.7     *Vital Signs, Physical Findings, and Other Safety Assessments***

##### **7.4.7.1     *Physical Examination***

A complete physical examination will be performed at Visit 1 (OLE Baseline/Week 24), Visit 6 (Week 52), Visit 10 (EoT/Week 106), and Safety Follow-Up Visit SFU-3 (Week 126), as indicated in Table 1. 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 OLE Baseline must be reported on the “Adverse Events Ongoing from Core Study” page of the eCRF. Significant findings detected after randomization to the OLE study that meet the definition of an AE must be recorded on the relevant “Adverse Event” page of the eCRF.

#### **7.4.7.2 Vital Signs**

Vital signs (temperature, heart rate, BP, and respiratory rate) will be measured as indicated in Table 1, 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.

#### **7.4.7.3 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. 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.

#### **7.4.7.4      *Cardiovascular Risk Assessment***

Cardiovascular risks factors (alcohol use with evaluation of average number of drinks consumed weekly, tobacco use with evaluation of average number of tobacco products consumed daily, central obesity, use of any lipid-lowering medication or any other CV agents, prior history of CV events and diabetes, family history of premature CV disease [age <55 years for males and <65 years for females], and other risks) will be recorded at the time points specified in Table 1. The CV risk assessment data will be provided to the CVAC for use in the review and adjudication of MACE (see Sections 5.2.1 and 7.4.4.2)

#### **7.4.7.5      *Electrocardiogram***

A standard 12-lead ECG will be performed at the time points specified in Table 1.

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).

#### **7.4.7.6      *Evaluation of Chest X-ray***

A chest X-ray (both lateral and posteroanterior) will be performed at all time points specified in Table 1. A chest X-ray need not be conducted if one has been performed and evaluated by a certified specialist to confirm the absence of TB or other pulmonary infection within 8 weeks prior to a specified timepoint, and if the films or images are available and included in the subject's source documents; 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 OLE Baseline and collected during the study should be evaluated by a certified specialist and kept as source documents.

#### **7.4.8          *Safety Monitoring***

R-Pharm International's designee will monitor safety data throughout the course of the study. The designee will review trends, laboratory data, and AEs at periodic intervals.

In the event that ongoing safety monitoring uncovers an issue that needs to be addressed at the treatment group level, members of the DSMB (an external advisory group for this study

formed to protect the integrity of data) can conduct analyses of unblinded safety data. See also Section 7.4.4 for details regarding the DSMB.

#### **7.4.9 Tuberculosis Risk Questionnaire**

The questionnaire “Tuberculosis Risk Questionnaire” (see Appendix 2 [Section 13.2]) should be used as a source document. The questionnaire will be completed at Visits 1 (OLE Baseline/Week 24), 4 (Week 36), 6 (Week 52), 8 (Week 76), 10 (EoT/Week 106), and SFU-2 (Week 112) as noted in Table 1.

If question No. 1 (Does the subject have a new diagnosis of active TB disease) of the TB risk questionnaire is answered with “Yes” at Visit 1 (OLE Baseline/Week 24), the subject is not allowed to enter the study (see exclusion criterion No. 2, 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 any visit after Visit 1 (OLE Baseline/Week 24), a “Yes” response 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 7.4.10).

This risk questionnaire is not to be used to exclude TB disease or confirm diagnosis.

#### **7.4.10 Management of Tuberculosis**

Subjects that 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 certified TB specialist or pulmonologist who is familiar with diagnosing and treating TB (as acceptable per local practice).

If active 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 7.4.5.5.

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 4 [Section 13.4]), and the subject agrees to complete the entire course of recommended LTBI therapy. Study treatment should not be administered until active TB is ruled out, the subject starts prophylactic LTBI therapy, and the Investigator receives confirmation from the Medical Monitor if the subject deviated from the allowed injection window. Confirmed latent TB should be recorded as an AE on the relevant pages of the eCRF. Details regarding follow-up of AEs are provided in Section 7.4.5.4.

## **7.5 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) (CHMP/International Council for Harmonisation [ICH]/135/1995), R-Pharm International and R-Pharm International'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
- Study site initiation visit
- Early study 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-Pharm International's (or designee's) Clinical Quality Assurance Department may conduct periodic audits of the study processes, including study site, study 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 International's designee and regulatory authorities.

### 8.1 Monitoring

R-Pharm's designee 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 International. Monitors will establish and maintain regular contact between the Investigator and R-Pharm International.

Monitors will evaluate the competence of each study site, informing R-Pharm International 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 study treatment 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 International 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).

For further details of study monitoring, please refer to the Clinical Operations Plan and the Pharmacy Monitoring Guidelines.

### **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 International'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 interobserver 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.



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 the 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.

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 study site 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 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.

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 a Quality Assurance audit during the course of the study by R-Pharm International or R-Pharm International's designee on behalf of R-Pharm International. In addition, inspections may be conducted by regulatory bodies at their discretion.

## 9. STATISTICS

### 9.1 Determination of Sample Size

All subjects who previously completed 24 weeks of double-blind treatment in the core studies will be eligible to enroll in this OLE study. It is estimated that approximately 1880 subjects will be randomized in the OLE study to 1 of 2 treatment groups (OKZ 64 mg q4w or OKZ 64 mg q2w) in a 1:1 ratio.

### 9.2 Data to be Analyzed

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

### 9.3 Analysis Populations

- **Safety Population:** The Safety population will include all subjects who receive at least 1 dose of study treatment during the OLE study. Subjects in the Safety population will be analyzed according to the treatment they actually received.
  - A combined analysis of safety data from all subjects participating in the core studies and the OLE study will be conducted separately and details will be included in a separate Statistical Analysis Plan (SAP) for an Integrated Summary of Safety (ISS). Results of the ISS will be reported separately and will not be included in the Clinical Study Report of this study.
- **Modified Intent-to-Treat (mITT) Population:** The mITT population will include all subjects who sign an ICF for participation in the OLE study, are randomized in the OLE study, and receive at least 1 dose of study treatment in the OLE study. Subjects will be analyzed according to the treatment group to which they were randomized in the OLE study. The mITT population will be the primary efficacy analysis population.
- **Per Protocol (PP) Population:** The PP population will include all mITT subjects who do not have any major protocol violations. Subjects will be analyzed according to the OLE treatment group to which they were randomized. Major protocol violations and the inclusion of subjects in the PP population will be finalized prior to database lock. The PP population will be used for supportive analyses of selected efficacy endpoints.

## 9.4 Statistical Methods

This section provides a high-level description of the analyses planned in this study. Details of any analysis, interim or final, will be specified in the SAP, to be written and finalized prior to database lock. The statistical analysis will be performed by R-Pharm International's designee. All statistical analyses will be conducted using SAS<sup>®</sup> version 9.2 or higher for Windows.

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

Data collected after the modification of background therapy (as described in Section 6.13.3) will be used in all analyses.

Data collected during the core studies for subjects enrolled in the OLE study may be programmatically combined with the OLE study database for selected analyses.

All analyses of safety and efficacy will be descriptive; no inferential analyses will be performed.

Continuous endpoints will be summarized using descriptive statistics such number of available values (n), mean, median, minimum, maximum, and standard deviation in each treatment group and overall, as appropriate. Categorical endpoints will be summarized by the number and percentage of subjects in each category.

Data will be summarized based on treatment groups reflecting randomized or actual treatment (for efficacy or safety analyses, respectively) during the core and OLE studies as follows:

- a. OKZ 64 mg q4w (OLE): All subjects in the OKZ 64 mg q4w group in the OLE
- b. OKZ 64 mg q2w (OLE): All subjects in the OKZ 64 mg q2w group in the OLE
- c. OKZ 64 mg q4w (core/OLE): Subjects from the OKZ 64 mg q4w group in the core study and continuing on OKZ 64 mg q4w in OLE. For subjects enrolling from the CL04041025 core study, inclusion in the OKZ 64 mg q4w group in the core study will be based on the initial treatment period prior to Week 16 (i.e., placebo subjects re-randomized to receive OKZ 64 mg q4w at Week 16 will not be included in this group).
- d. OKZ 64 mg q2w (core/OLE): Subjects from the OKZ 64 mg q2w group in the core study and continuing on OKZ 64 mg q2w in OLE. For subjects enrolling from the CL04041025 core study, inclusion in the OKZ 64 mg q2w group in the core study will be based on the initial treatment period prior to Week 16 (i.e., placebo subjects

- re-randomized to receive OKZ 64 mg q2w at Week 16 will not be included in this group).
- e. Placebo – OKZ 64 mg q4w (OLE): Subjects from the placebo group in the core studies CL04041022 and CL04041023 that are assigned to the OKZ 64 mg q4w in the OLE.
  - f. Placebo – OKZ 64 mg q2w (OLE): Subjects from the placebo group in the core studies CL04041022 and CL04041023 that are assigned to the OKZ 64 mg q2w in the OLE.
  - g. Placebo – OKZ 64 mg q4w (core/OLE): Subjects from the placebo group in the core study CL04041025 (through Week 14) that are re-randomized to the OKZ 64 mg q4w group starting at Week 16 of the core study and continuing on OKZ 64 mg q4w in OLE.
  - h. Placebo – OKZ 64 mg q2w (core/OLE): Subjects from the placebo group in the core study CL04041025 (through Week 14) that are re-randomized to the OKZ 64 mg q2w group starting at Week 16 of the core study and continuing on OKZ 64 mg q2w in OLE.
  - i. Adalimumab – OKZ 64 mg q4w (OLE): Subjects from the adalimumab group in the core study CL04041023 that are assigned to the OKZ 64 mg q4w group in the OLE.
  - j. Adalimumab – OKZ 64 mg q2w (OLE): Subjects from the adalimumab group in the core study CL04041023 that are assigned to the OKZ 64 mg q2w group in the OLE.

Subjects are considered to be part of the placebo group during the core study if they are randomized to or receive placebo as their overall study treatment, and not as monthly placebo injections administered to maintain the blind in the OKZ 64 mg q4w treatment groups.

Note that treatment groups (c) through (j) are mutually exclusive; treatment groups (a) and (b) are aggregates representing all subjects treated with a specific OKZ regimen during the OLE study, regardless of the treatment received during the core study.

Additional summaries of efficacy endpoints may be generated for subjects from each core study separately, which will be detailed in the SAP.

#### **9.4.1 Definition of Baseline**

Unless otherwise specified, data will be analyzed for changes from both Core Baseline and OLE Baseline values. The Core Baseline value for each parameter will be defined as the baseline value from the core study (i.e., the last available measurement prior to the first dose

of study treatment in the core study). The OLE Baseline value will be defined as the last available measurement prior to the first OLE dose of study treatment. For subjects from Study CL04041025 who receive placebo through Week 14 and are re-randomized to OKZ starting at Week 16 (groups [g] and [h] as defined in Section 9.4), additional analysis of change from the last pre-OKZ value (prior to the first dose of OKZ at Week 16) will also be performed.

#### **9.4.2 Disposition of Study Subjects**

Disposition of study subjects will be summarized by treatment group (defined in Section 9.4) as the number and percentage of subjects enrolled (signed ICF for participation in the OLE study), randomized in the OLE study, included in each analysis population as defined in Section 9.3, completing the study treatment, and discontinuing from the study treatment overall and by reason for discontinuation, as well as completing the Safety Follow-Up Period or discontinuing during the Safety Follow-Up Period. 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, where the time to treatment discontinuation will be calculated as the number of days from randomization at enrollment in the OLE study to the last dose of OLE study treatment. Subjects who complete the open-label Treatment Period as planned through Visit 10 (EoT/Week 106) will be censored on the date of their last dose in the OLE study.

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

#### **9.4.3 Demography and Baseline Characteristics**

Demographic information and baseline characteristics collected at baseline of the core studies will be summarized for the treatment groups defined in Section 9.4. Key subject assessments at the time of enrollment in the OLE study (e.g., selected laboratory/safety assessments, ACR components, DAS28 [CRP], etc.) will also be summarized.

#### **9.4.4 Prior and Concomitant Medications**

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

Any medication that a subject started before the first dose of OLE study treatment and continued to take during the OLE study, and any medication that the subject began taking after the first dose of the OLE study treatment, will be classified as concomitant.

Medications administered as a change in background therapy (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 group.

Medications administered concomitantly during the core studies or prior to the core studies may also be summarized.

#### **9.4.5 Exposure and Compliance**

Exposure to the OLE study treatment and compliance will be summarized descriptively by treatment group (see Section 9.4) for the Safety population based on treatment administration records in the Subject Diary and the return of used/unused study treatment (vials and/or PFS cartons) to the study site.

For a given study period, exposure to open-label study treatment will be calculated as the number of doses received during the open-label study period. The number of doses received will be calculated as a maximum of the number of injections recorded in the Subject Diary and the number of used vials and/or used PFS cartons returned by the subject to the study site.

Duration of exposure will be defined as the total number of days a subject was exposed to study treatment in the open-label Treatment Period, calculated as:

$$\text{Date of last open-label dose} - \text{Date of first open-label dose} + 1 \text{ day}$$

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

$$(\text{Exposure to open-label study treatment} / \text{number of doses subject was expected to receive}) \times 100$$

Compliance will be calculated based on all planned doses (through completion or early discontinuation of treatment), as appropriate for each treatment group.

#### **9.4.6 Safety Analyses**

Analysis of safety endpoints (see Section 4.1) will be based on the Safety population. Subjects in the Safety population will be analyzed according to the treatment they actually received.

All safety and tolerability data recorded during the study will be listed and summarized descriptively by the treatment groups described in Section 9.4, and over time, as appropriate. No imputation for missing safety data will be performed. Further details will be provided in the SAP.

All continuous safety parameters will be summarized at each OLE visit in terms of actual values at each time point, changes from Core Baseline values, and changes from OLE Baseline values, as appropriate. All categorical safety parameters will be summarized in terms of number and percent of subjects in each category by OLE visit. Core Baseline and OLE Baseline values will also be summarized for reference. For subjects from Study CL04041025 who receive placebo through Week 14 and are re-randomized to OKZ starting at Week 16 (groups [g] and [h] as defined in Section 9.4), additional analysis of change from the last pre-OKZ value (prior to the first dose of OKZ at Week 16) will also be performed.

Major components for the safety analysis will include:

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

In addition to the primary safety analysis, the incidence of AEs may be analyzed separately for subjects administered additional DMARDs (assigned as rescue medication during the core studies) and for subjects not receiving additional DMARDs as rescue medication.

#### **9.4.6.1     *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 latest 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.

An AE will be defined as treatment-emergent in the OLE study if its onset date or worsening in severity is on or after the date of first administration of the OLE study treatment. In cases



where only partial information is available for the onset date of an AE, available date components will be used to determine treatment-emergent status; in the case of ambiguity, AEs will be considered treatment-emergent.

The following summaries of subject incidence and number of events will be presented by the treatment groups defined in Section 9.4:

- Overall summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of serious TEAEs by SOC and PT
- Summary of TEAEs leading to death by SOC and PT (if applicable)
- Summary of treatment-emergent AESIs (as defined in Section 7.4.3) by SOC and PT
- Summary of (adjudicated) MACE and individual MACE components
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of drug-related TEAEs by SOC and PT
- Summary of TEAEs leading to early treatment discontinuation by SOC and PT
- Summary of the most common TEAEs by PT ( $\geq 5\%$  in any treatment group)
- Summary of TEAEs by Standardized MedDRA Queries narrow terms

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

#### **9.4.6.1.1 Analysis of Treatment-Emergent Adverse Event Rates per 100 Patient-years of Follow-up**

Summaries of TEAEs occurring in subjects in the safety population of this OLE study will also be provided based on combined AE data from the core studies and the OLE study, attributing each TEAE to the last study treatment received at/before the AE onset. In other words, an AE will be defined as treatment-emergent under a given study treatment (OKZ 64 mg q4w, OKZ 64 mg q2w, placebo, or adalimumab) if AE's onset date is on or after the date of first dose the corresponding treatment and prior to initiation of the next study treatment, if any (e.g., OKZ after placebo or adalimumab). In order to account for differences in the duration of exposure and follow-up under each study treatment and across subjects, subject IRs and ERs will be summarized per 100 subject-years (SY) of follow-up (/100 SY) based on the OLE safety population and presented by study treatments as follows:

- i. OKZ 64 mg q4w: subjects receiving OKZ 64 mg q4w during the core study or OLE. Only those TEAEs that first occur or worsen in severity after the first administration of OKZ 64 mg q4w (either in the core or OLE study) will be counted.
- ii. OKZ 64 mg q2w: subjects receiving OKZ 64 mg q2w during the core study or OLE. Only those TEAEs that first occur or worsen in severity after the first administration of OKZ 64 mg q2w (either in the core or OLE study) will be counted.
- iii. Placebo: subjects receiving placebo during the core study. Only those TEAEs that first occur or worsen in severity after the first administration of placebo and prior to administration of OKZ will be counted. Subjects are considered as receiving placebo during the core study if they are receiving placebo as their overall study treatment, and not as monthly placebo injections administered to maintain the blind in the OKZ 64 mg q4w group.
- iv. Adalimumab: subjects receiving adalimumab as active control study treatment during the core study CL04041023. Only those TEAEs that first occur or worsen in severity after the first administration of adalimumab and prior to administration of OKZ will be included.

The following summaries will be provided:

- IRs (/100 SY) and ERs (/100 SY) for TEAEs overall and by SOC
- IRs (/100 SY) and ERs (/100 SY) for SAEs overall and by SOC and PT
- IRs (/100 SY) and ERs (/100 SY) for AESIs overall and by SOC and PT
- IRs (/100 SY) and ERs (/100 SY) for (adjudicated) MACE and individual MACE components
- IRs (/100 SY) and ERs (/100 SY) for most frequent TEAEs (PT level IRs [/100 SY]  $\geq 5.0$  in any treatment group) by SOC and PT

IRs/100 SY for each specific AE term (referred to as “event” for brevity) under treatment  $j$ , corresponding to treatments (i) – (iv) described above, will be calculated as follows:

$$IR_j (/100 SY) = s_j / \sum_i c_{i,j}$$

where  $s_j$  is the number of subjects with the event that is treatment-emergent under treatment  $j$ , and  $c_{i,j}$  is a truncated follow-up time (in 100-year units) for subject  $i$  and treatment  $j$  (i.e., the time from the subject’s date of first dose of treatment  $j$  to the date of first occurrence of the event after start of treatment  $j$  or end of follow-up period for treatment  $j$ , whichever

occurs earlier). For OKZ treatments (OKZ 64 mg q4w and q2w), the end of follow-up period will be the date of last dose of OKZ treatment plus 155 days (5 half-lives of study treatment) or last contact with the subject, whichever occurs earlier. For placebo and adalimumab treatments, the end of follow-up period will be the day before the start of OKZ treatment.

ERs (/100 SY) for each specific AE term under treatment  $j$  will be calculated as follows:

$$ER_j (/100 SY) = \sum_i v_{i,j} / \sum_i t_{i,j}$$

where  $v_{i,j}$  is the number of treatment-emergent events that the subject  $i$  experiences under treatment  $j$ , and  $t_{i,j}$  is a total follow-up time (in 100-year units) of subject  $i$  for treatment  $j$ , i.e., from the date of subject's first dose of treatment  $j$  to the end of follow-up period for treatment  $j$ . For OKZ treatments (OKZ 64 mg q4w and q2w), the end of follow-up period will be the date of last dose of OKZ treatment plus 155 days (5 half-lives of study treatment) or last contact with the subject, whichever occurs earlier. For placebo and adalimumab treatments, the end of follow-up period will be the day before the start of OKZ treatment.

Assuming the event process is Poisson distributed, exact  $100*(1-\alpha)\%$  confidence intervals for  $IR_j$  (/100 SY) and  $ER_j$  (/100 SY) will be calculated as follows (Sahai and Khurshid, 1993):

$$\text{Lower confidence limit: } LCL = \frac{\chi^2_{\alpha/2, 2D}}{2E} \text{ for } D > 0, 0 \text{ otherwise,}$$

$$\text{Upper confidence limit } UCL = \frac{\chi^2_{1-\alpha/2, 2D+2}}{2E}$$

where  $\chi^2_{\alpha, k}$  is the  $\alpha^{\text{th}}$  quantile of the Chi-square distribution with  $k$  degrees of freedom, and the  $D$  and  $E$  are the numerator and denominator of the rate.

Summaries of  $IR_j$  (/100 SY) and  $ER_j$  (/100 SY) for the OKZ treatments (i) and (ii) may be further subdivided into 2 subgroups: subjects receiving adalimumab in the core study CL04041023 versus all other subjects.

In addition to the above summaries of rates/100 SY, a plot of cumulative mean function (CMF) across study follow-up time will be produced for selected types of events for each treatment (i) – (iv). The cumulative mean function at each time point  $t$  represents an estimated mean number of recurrent events expected by time  $t$  in a treatment group (Siddiqui, 2009; Nelson, 2003). Plots of CMF will be produced for SAEs overall and by SOC, AESIs overall and by SOC, as well as MACEs.

#### 9.4.6.1.2 Time to First Major Adverse Cardiovascular Event

For MACEs and individual components of MACE, time from the first dose of OKZ to first event will be summarized using a Kaplan-Meier product limit method. This analysis will be

based on the OLE Safety population using combined data from the core studies and the OLE study.

Time to first event will be computed for each specific type of event (MACE overall and individual components of MACE) as the number of days between the subject's date of first dose of OKZ treatment either in the core or OLE study and the onset of the first event that is treatment-emergent under the OKZ treatment. Subjects not experiencing an event of interest during the follow-up period associated with the OKZ treatment will be censored at the date of last contact.

Summaries will be presented by treatment groups, as defined in Section 9.4. Summaries will include plots of the estimated survival curves using the Kaplan-Meier method as well as Kaplan-Meier cumulative estimates of event-free rates at time points corresponding to 6, 12, 18, 24, and 30 months after initiation of OKZ treatment. Pointwise confidence intervals for these estimates will be computed using the log-log transformation method. Kaplan-Meier estimates of mean event-free time and its log-log transformed confidence interval in each treatment group will also be produced. A time limit of 127 weeks will be used for the estimation of mean event-free time if the largest observed time in data is censored. Descriptive statistics for the number of subjects with event, censored, and duration of follow-up for censored subjects will be provided.

Additional details will be provided in the SAP.

#### **9.4.6.1.3 Time to First Malignancy**

Analysis of time from the first dose of OKZ to the first malignancy will also be conducted using the Kaplan-Meier method in a similar manner as will be done for MACE (see Section 9.4.6.1.2).

#### **9.4.6.2 Other Safety Analyses**

All clinical laboratory, vital signs, ECG, and physical examination data collected during the study will be summarized descriptively by treatment groups described in Section 9.4, and study visit, as appropriate. Continuous safety parameters will be summarized in terms of actual values at each time point, and if appropriate, changes from the Core Baseline values, changes from OLE Baseline values, and changes from the last pre-OKZ values (see Section 9.4.1). Categorical parameters will be summarized in terms of the number and percent of subjects in each category by visit.

Laboratory values will be flagged as low, normal, or high relative to the normal range of each test. Laboratory results will also be graded according to the CTCAE criteria (version 4.0) and will be considered as markedly abnormal if they meet the criteria of Grade 3 or higher.

The number and percent of subjects with treatment-emergent chemistry and hematology abnormalities (low or high) as well as with CTCAE Grade  $\geq 2$  results after the first dose of OLE study treatment will be summarized by laboratory parameter and by visit as well as during the OLE study overall based on the most extreme subject values.

The number and percent of subjects with clinically significant urinalysis abnormalities will be summarized by parameter (specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase) by visit as well as during the OLE study overall based on the most extreme subject values.

Liver function parameters (AST, ALT, alkaline phosphatase, and total bilirubin) will be summarized categorically using different levels of elevation thresholds (multiples of normal range upper limit) as well as according to the criteria of Hy's Law.

Lipid parameters (total cholesterol, HDL, LDL, and triglycerides) will be summarized by means of descriptive statistics for the actual values and changes from Core Baseline and OLE Baseline over time.

Clinically significant changes in vital signs will be identified and summarized for changes from the Core Baseline values, OLE Baseline values, and last pre-OKZ values (see Section 9.4.1).

Categorical ECG findings (normal; abnormal, not clinically significant; and abnormal, clinically significant) will be summarized at each visit.

#### **9.4.7 Analysis of Efficacy Endpoints**

Analysis of efficacy endpoints (see Sections 4.2) and PROs (see Section 7.1) will be based on the mITT population. Supportive analyses will also be done using the PP population for the ACR20/50/70, SDAI  $\leq 3.3$ , and DAS28 (CRP)  $< 3.2$  endpoints.

All summaries will be presented by the treatment groups defined in Section 9.4, based on randomized treatment.

All continuous efficacy and PRO endpoints will be summarized at each OLE visit in terms of actual values, changes from Core Baseline values, changes from OLE Baseline values, and changes from the last pre-OKZ values (see Section 9.4.1). All categorical parameters and responder-type endpoints will be summarized in terms of number and percent of subjects in each category by OLE visit. Core Baseline values, OLE Baseline values, and the last pre-OKZ values will also be summarized for reference. Graphical summaries will also be presented for mean actual values over time by treatment group for selected endpoints (e.g., DAS28 [CRP]).

Binary endpoints that are based on changes from baseline (e.g., ACR20) will be analyzed based on changes from Core Baseline values, OLE Baseline values, and changes from the last pre-OKZ values.

Missing efficacy data resulting from missed intermediate visits will be handled as described in Section 9.4.8.

Missing data resulting from early treatment discontinuation will not be imputed, unless otherwise specified. For binary efficacy endpoints, in addition to analyses based on observed data, summaries will also be provided considering all subjects who discontinue the OLE study treatment early as nonresponders at all post-discontinuation scheduled time points.

#### **9.4.8 Handling of Missing Data**

Missing efficacy data resulting from missed intermediate visits will be imputed from the surrounding visits. For binary efficacy endpoints, 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.

Missing efficacy data resulting from early treatment discontinuation will not be imputed.

Missing safety data will not be imputed.

#### **9.4.9 Pharmacokinetic/Pharmacodynamic Correlations**

No PK/PD correlations are planned for this study.

#### **9.4.10 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.

## **9.5 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 detail 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 7.4.4.

## **9.7 Interim Analysis**

For any interim data cuts or analyses which occur, the details will be specified in the SAP.

## **10. ETHICS**

### **10.1 Institutional Review Board/Independent Ethics Committee**

An IRB/IEC should approve the final protocol, including the final version of the ICFs and any other written information and/or materials to be provided to the subjects. The Investigator will provide R-Pharm International or R-Pharm International'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 International or its designee before enrollment of any subject into the study.

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

R-Pharm International 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 International 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., ICF for subjects and a separate ICF for caregivers [if applicable]) 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 ICFs contains 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 ICFs 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 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 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 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 International or R-Pharm International'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 International and R-Pharm International'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 +1 512 652 0191 or +1 973 659 6677 or +3 318 699 0019).

### **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 International
- Resolution of data queries
- Accountability, reconciliation, and arrangements for unused study treatments
- 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 International, or regulatory agencies as part of their duties to ensure that research subjects are protected.

R-Pharm International 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 noncompliance. If R-Pharm International determines such action is needed, R-Pharm International will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, R-Pharm International will provide advance notification to the Investigator of the impending action prior to its taking effect.

R-Pharm International 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 International or its designee. In addition, arrangements will be made for return of all unused study treatments in accordance with R-Pharm International'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 International.

## **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 International, who agrees to abide by the retention policies. Written notification of transfer must be submitted to R-Pharm International. The Investigator must contact R-Pharm International prior to disposing of any study records.

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

## **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 International'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 the 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 International will sign the protocol to confirm this agreement.

The Investigator is encouraged to discuss the withdrawal of a subject, from either treatment or study, with R-Pharm International or R-Pharm International's designee, in advance, whenever is possible. In addition, any case when a subject deviated from the dosing schedule or missed any scheduled treatment should be reported to R-Pharm International and/or R-Pharm International's designee promptly, for making decision whether the study participation should be continued.

Medical Monitor should be contacted before restarting the study treatment after any interruption of study treatment. Medical Monitor should be contacted in case of potential hepatotoxicity events that fulfill any of the criteria of seriousness to investigate all potential causes of liver toxicity (see Section 7.4.3.4).

### **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 International 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 the ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any study site where the Investigator has not signed the protocol.

### **11.6.3 Publication Policy**

R-Pharm International 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 (study 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 International.

## **11.7 Financing and Insurance**

R-Pharm International is the Sponsor of the study. R-Pharm International 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 International 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.

## 12. REFERENCES

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## **13. APPENDICES**



### 13.1 Appendix 1: Methotrexate Dose Reduction Guidelines

ALT and/or AST	Total Bilirubin	Repeat Laboratory	MTX	Study Treatment
1× to ≤2× ULN	NA	No need	No change	No change
>2× to ≤3× ULN	NA	Within 1 week	No change or can consider reduction in dose	No change
If repeat >2× to ≤3× ULN	NA	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, 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 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, 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 until LFTs normalize or return to baseline and consider restarting at lower dose	Hold and consider restarting after discussion with the R-Pharm International Medical Advisor or designee
>3× ULN accompanied by symptoms which, as determined by the Investigator, are the result of hepatic injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, 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

ALT and/or AST	Total Bilirubin	Repeat Laboratory	MTX	Study Treatment
>5× ULN for for ≥2 consecutive 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
>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; LFTs = liver function tests; NA = not applicable; ULN = upper limit of normal.

## 13.2 Appendix 2: Tuberculosis Risk Questionnaire

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

Physician's signature: \_\_\_\_\_

**Table 5 List of Endemic TB Countries (Incidence >50/100,000)**

Country	Incidence <sup>a</sup>	Country	Incidence <sup>a</sup>	Country	Incidence <sup>a</sup>
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)
Democratic Republic of	325 (295–356)	Mauritania	111 (79–148)	Thailand	171 (90–276)

Country	Incidence <sup>a</sup>	Country	Incidence <sup>a</sup>	Country	Incidence <sup>a</sup>
Congo					
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)

Abbreviation: 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.

### 13.3 Appendix 3: Clinical Criteria for Diagnosing Anaphylaxis

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

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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 1 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<sup>a</sup>
  - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

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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.

## 13.4 Appendix 4: Recommendations for Management of Latent Tuberculosis Infection

Recommendations for management of latent tuberculosis infection (LTBI) are provided below. If the known source of a subject's LTBI is an individual with drug-resistant TB, these recommended treatments must be modified after consultation with a certified TB specialist or pulmonologist who is familiar with treating TB, as acceptable per local practice.

### Adapted CDC Recommendations for Management of Latent TB

Drug(s)	Duration	Interval	Comments
Isoniazid	9 months	Daily Twice weekly <sup>a</sup>	
Isoniazid	6 months	Daily Twice weekly <sup>a</sup>	This regimen is not preferred for TB prophylaxis and should not be used in this study.
Isoniazid and Rifapentine	3 months	Once weekly <sup>a</sup>	
Rifampin	4 months	Daily	

Abbreviations: CDC = Centers for Disease Control and Prevention; TB = tuberculosis.

a. Use Directly Observed Therapy (DOT).

## **13.5 Appendix 5: Protocol Amendment 2 Summary of Changes**