TITLE PAGE

Protocol Title:

A Phase 1, Open-label, Study in Subjects with Rheumatoid Arthritis to Evaluate the Effect of a Single Dose of Olokizumab on the Pharmacokinetics of Substrates for CYP1A2, CYP2C9, CYP2C19, and CYP3A4

Protocol Number: CL04041026

Amendment Number: Amendment 3

Product: Olokizumab

Study Phase: Phase 1

Sponsor Name: R-Pharm International

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Regulatory Agency Identifying Number: IND 104933

Date of Protocol: 22 September 2021

Sponsor Signatory:

I hereby confirm that Protocol CL04041026 "A Phase 1, Open-label Study in Subjects with Rheumatoid Arthritis to Evaluate the Effect of a Single Dose of Olokizumab on the Pharmacokinetics of Substrates for CYP1A2, CYP2C9, CYP2C19, and CYP3A4" is created in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline, current revision and all applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations, as well as Order No. 200n dated April 01, 2016 of the Ministry of Health of the Russian Federation on Approval of Rules for GCP.

Mikhail Samsonov*	**Date**
Chief Medical Officer	
R-Pharm	

*Signing the protocol on behalf of R-Pharm International by power of attorney #16 dated 02 November 2020.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

Document	Date	Substantial	Region
Amendment 3	22-September-2021	Yes	Global
Amendment 2	11-May-2021	Yes	Global
Amendment 1	21-Sep-2020	Yes	Global
Original Protocol	14-Oct-2019	-	-

Amendment 3 (22-September-2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment (Amendment 3) is to improve enrolment by reducing screen failure and possibly enhance further pharmacokinetic analysis. Thus, a maximum age of inclusion is increased to 70 years, lower limits of weight are decreased to 55 in males and 45 in females; a permission to participate in the study is made for females of childbearing potential (with the requirement for highly effective contraception adherence); subjects with the CYP2C9 *1/*2 and *1/*3 genotypes (which could be considered as intermediate instead of poor metabolizers) are considered eligible; subjects are considered eligible with hemoglobin level of 95 g/L and higher; subjects with positive anti-HBc antibodies test (and negative HBsAg and HBV DNA tests) are considered eligible upon hepatologist conclusion that no additional risk is suspected; subjects with NYHA Class II heart failure are made eligible (see Table 2 for each change implemented rationale description).

Amendment 2 (11 May-2021)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Previous amendment (Amendment 1) was introduced due to global spread and the severity of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The purpose of this amendment (Amendment 2) was to keep proactive measures to exclude subjects with COVID-19 who may be contagious to prevent further transmission but to allow inclusion of patients with a history of this condition, vaccine administration, as well as increasing the upper age limit for enrollment. These changes are

necessitated due to the changed environmental conditions of COVID-19, including improved prophylaxis and treatment. Few changes related to patients' genotype assessment and analysis of the data were included to improve enrolment and possibly enhance further pharmacokinetic analysis.

Amendment 1 (21-September-2020)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially detected as a pneumonia of unknown cause in Wuhan, China and declared a pandemic due to its global spread and the severity of disease. The purpose of this amendment was to implement proactive measures to exclude subjects with COVID-19 or a history thereof and to add testing to identify such subjects at the earliest stage of infection. Screening tests are intended to identify infected individuals without, or prior to development of, symptoms who may be contagious so that measures can be taken to prevent further transmission and proper treatment may be implemented as per the local guidelines.

Table 2 Description of Changes in Amendment

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis: Overall Design	Added physical examination and FSH testing as Screening-Stage 1 procedures.	In accordance with changes made for SoA (Table 3) and Section 4.1. Overall Design.
1.1 Synopsis: Diagnosis and Main Criteria for Inclusion	Maximum age of inclusion updated from 65 to 70 years.	In accordance with changes made for the Section 5.1 Inclusion Criteria.
	Lower limits for weight was updated from 60 to 55 kg in males and from 50 to 45 kg in females.	In accordance with changes made for the Section 5.1 Inclusion Criteria.
	Deleted "of nonchildbearing potential' from female subjects eligibility description.	In accordance with changes made for the Section 5.1 Inclusion Criteria.
	Added contraception requirements for male and female subjects in the study.	
1.3 Schedule of Activities – Table 3	An explanation (footnote) for a Joint count (DAS28) and Patient Global Assessment of Disease Activity (Visual Analog Scale – Bullet Scale) – was added on Day 1 and Day 8.	To establish consistency with the Table 9.
	An explanation (footnote) for a physical examination – was added on Day 22.	
	FSH testing was moved to the Screening-Stage 1.	To provide the FSH test results available at Screening-Stage 2 so that pregnancy test to be made only for WOCBP.
	A pregnancy test assessment – blood test - for female subjects determined as WOCBP was added on Screening-Stage 2 with applicable footnote.	In accordance with changes made for the Sections 5.1. Inclusion Criteria and 5.2 Exclusion Criteria - To provide eligibly compliance at screening.
	A pregnancy test assessment – urine test - for female subjects determined as WOCBP was added on Day (-1), Day 8, Day 21, EOT and EOS visits with applicable footnote.	In accordance with changes made for the Sections 5.1. Inclusion Criteria and 5.2 Exclusion Criteria - For pregnancy monitoring of female subjects of childbearing potential throughout the study to avoid pregnancies.
	A HBV DNA test was added to the viral serology screening procedure and applicable footnote was corrected accordingly.	In accordance with changes made for the Sections 5.2 Exclusion Criteria – to allow inclusion of anti-HBc positive subjects in case of HBV DNA test is negative – i.e. there is no active infection.
	INR only procedure was added on Day 5.	To establish consistency with the Table 9 and Section 8.1.4 Clinical Safety Laboratory Assessments

Section # and Name	Description of Change	Brief Rationale
	AEs/SAEs recording procedure was added on Screening-Stage1.	To establish consistency with the footnote and Section 8.2 Adverse Events as these specify that all events are to be reported from the signature of the ICF.
	A footnote regarding pregnancy test performance in the study for WOCBP only was added.	To make procedure performance clear.
	Footnote z (previously y) was corrected – the excessive information was deleted.	A part of clarification is already provided in the footnote x (previously w) and is applicable to the entire procedure.
2.2.2 Clinical Data	Information regarding completed and ongoing clinical studies were updated: number of studies, designs descriptions, summary of PK, safety and efficacy results available.	According to the latest IB edition (ed.12).
2.3 Benefit/Risk Assessment	Efficacy conclusion was updated with available data from completed and ongoing studies.	In accordance with changes made for Section 2.2.2 Clinical Data.
4.1 Overall Design	Added physical examination and FSH testing as Screening-Stage 1 procedures.	To establish consistency with the SoA (Table 3).
4.2 Scientific Rationale for Study Design	Description of female subjects' eligibility was corrected.	In accordance with changes made for the Section 5.1 Inclusion Criteria.
5.1 Inclusion Criteria	Maximum age of inclusion updated from 65 to 70 years.	To improve enrollment since the elderly age ranges from 60 to 74 (based on the WHO data), subjects of 70 years of age (inclusively) could be enrolled if the investigator considers no safety issues based on screening results for such subject.
	Incl.#2 was updated - WOCBP were made eligible for the study.	To improve enrollment since RA is known to be more prevalent in women.
	Incl.#3 was added - Contraception requirements were added for WOCBP in the study (female subjects or female partners of male subjects). WONCBP to be identified as previously described.	In accordance with changes made for Incl.#2 – To avoid pregnancies of WOCBP in the study due to the possible effects of study drug on the course and outcomes of pregnancy, since WOCBP were made eligible.
	Incl.#4 (prev. #3) was updated – lower limits for weight was updated from 60 to 55 kg in males and from 50 to 45 kg in females.	To improve enrollment since subjects with chronic inflammatory processes (which are the desired population of this study) have a tendency to lost in weight and to acquire cachectic appearance. Thus, such subjects could be enrolled if the investigator considers no safety issues

Section # and Name	Description of Change	Brief Rationale
		based on screening results for such subject.
	Incl.#8 was added - Female subjects of childbearing potential must have negative pregnancy test at Screening and throughout the study until the end of study (EOS, Day 161).	In accordance with changes made for Incl.#2 – To avoid pregnancies of WOCBP in the study due to the possible effects of study drug on the course and outcomes of pregnancy, since WOCBP were made eligible.
5.2 Exclusion Criteria	Excl.#18 was updates - Presence of CYP2C9 genotypes *1/*2 and *1/*3 were deleted from the Exclusion criteria.	According to the literature data these genotypes could be considered as intermediate instead of poor metabolizers, thus could present evident signs of CYP activity alteration after the study drug administration and be informative for the study assessments.
	Excl.#19 was updated with clarification that subjects previously participated in this or other OKZ study should be excluded only in case of receiving at least one OKZ dose.	To allow rescreening for subjects previously participated in this or other OKZ study but excluded from the study for some reason before any OKZ exposure.
	Excl.#20 was corrected – hemoglobin level applicable for inclusion was changed to 95 g/L and higher.	To improve enrollment – since anemia is a common finding for RA subjects, Thus such subjects could be enrolled if the investigator considers no safety issues based on screening results for such subject.
	Excl,#21 was corrected – a test for HBV DNA is added for anti-HBc positive subjects only; anti-HBc positive (solely or together with anti-HBs antibodies) subjects are made eligible unless HBsAg or HBV DNA positive and upon hepatologist consultation with documented conclusion no additional risk is suspected for the subject.	To improve enrollment - since single-dose administration of investigational drug (OKZ) is planned only no increase in risks is anticipated for the subjects with hepatitis in history or latent hepatitis (i.e. not active), assuming proper examination by hepatologist and his conclusion if the subject could participate in the study.
	Excl.#27 was corrected – subjects with NYHA Class II heart failure are made eligible.	To improve enrollment – since no increase in cardiovascular complications risk was shown for the investigational drug (OKZ) administration in previous phase 3 clinical trials (based on the assessment of the Cardiovascular Adjudication Committee). Thus, such subjects could be enrolled if the investigator considers no safety issues based on screening results for such subject.

Section # and Name	Description of Change	Brief Rationale
	Excl.#46 was added – pregnant and breastfeeding women are not eligible for the study.	In accordance with changes made for Incl.#2 – To avoid pregnancies and breastfeeding of WOCBP in the study due to the possible effects of study drug on the course and outcomes of pregnancy and breastfeeding, since WOCBP were made eligible.
5.3.3 Contraception	Requirement to adhere contraception in the study is added for WOCBP.	In accordance with changes made for the Section 5.1 Inclusion Criteria and Appendix 6.
7.1 Discontinuation of Study Treatment	Permanent Discontinuation of Study Treatment is marked as a separate section.	To make Discontinuation of Study Treatment criteria clearer.
	A clarification was added on procedures to be performed in case of early treatment discontinuation by subject – EOS visit should be performed after the EOT and SFU visits completion for this subject.	To make early treatment discontinuation process clearer.
7.1.2 Permanent Discontinuation of Study Treatment	Criteria for the permanent discontinuation of study treatment were corrected.	To make early treatment discontinuation process clearer.
	Pregnancy of female subject is added as a criteria for subject discontinuation from the study treatment.	In accordance with changes in the Section 5.2 Exclusion Criteria.
7.2 Subject Discontinuation/Withdrawal from the Study	Investigator's right to stop the study is added as a criteria for subject discontinuation.	To establish consistency with the Appendix 2.
	Other criteria for subject discontinuation/withdrawal from the study were corrected.	Since the criteria provided in the new version are applicable for the study discontinuation only (no other procedures to be made for the subjects after study discontinuation except EOS visit).
8.0 Study Assessments – Table 9	AEs/SAEs recording procedure was added on Screening-Stage1.	To establish consistency with the SoA (Table 3) and Section 8.2 Adverse Events as these specify that all events are to be reported from the signature of the ICF.
	Moved FSH testing to Screening-Stage 1.	In accordance with changes made for the Section 4.1 Overall Design and SoA (Table 3).
	A pregnancy test assessment for female subjects of childbearing potential was added on Screening-Stage 2 (blood), urine: Day (-1), Day 8, Day 21, EOT and EOS visits.	In accordance with changes made for the Section 5.2 Exclusion Criteria and SoA (Table 3).

Section # and Name	Description of Change	Brief Rationale
	COVID-19 RT-PCR testing in Period 1 was corrected to be made on Day 5 only; excessive explanation was deleted.	To establish consistency with SoA (Table 3); the test performance clarification is already in place within e footnote which is applicable to the entire procedure.
	Admission procedure is added on Day 21	To make procedures performance on this Day clearer.
8.1.4 Clinical Safety Laboratory Assessments	Added a clarification that RT-PCR testing should be comprised of two consecutive tests within approximately 36 hours.	To establish consistency with other applicable part of the protocol and make the procedure performance clearer.
8.2.6 Reporting and Follow-up Requirements for Pregnancies	Additional reporting and follow-up requirements for pregnancies in female subjects (WOCBP) were added.	In accordance with changes made for the Section 5.1 Inclusion Criteria – To provide proper safety monitoring in case of pregnancies since WOCBP were made eligible for the study.
8.6 Genetics	CYP2C9 genotypes *1/*2 and *1/*3 were described as intermediate metabolizers.	In accordance with changes made for the Section 5.2 Exclusion Criteria.
Appendix 3 Clinical Laboratory Tests – Table 14	Added HCG urine test for pregnancy exclusion in WOCBP.	In accordance with changes made for the Section 5.2 Exclusion Criteria and SoA (Table 3).
	A HBV DNA test was added to the viral serology screening procedure with an applicable footnote.	In accordance with changes made for the Section 5.2 Exclusion Criteria and SoA (Table 3).
Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information	Added contraceptive guidance for female subjects (WOCBP).	In accordance with changes made for the Section 5.1 Inclusion Criteria – To avoid pregnancies of WOCBP in the study due to the possible effects of study drug on the course and outcomes of pregnancy, since WOCBP were made eligible.
	Description of collection of pregnancy information was corrected.	In accordance with changes made for the Section 5.1 Inclusion Criteria and Section 8.2.6 Reporting and Follow-up Requirements for Pregnancies – To provide proper safety monitoring in case of pregnancies since WOCBP were made eligible for the study.
Throughout document	Minor editorial updates were made.	To established consistency throughout document and compliance with template and Style Guide.

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; CYP = cytochrome; EOS = end of study; EOT = end of treatment; FSH = follicle-stimulating hormone; HCG = human chorionic gonadotropin; IB = investigational brochure; ICF = informed consent form; IgG = Immunoglobulin G; IgM = Immunoglobulin M; OKZ = olokizumab; PK = pharmacokinetic; RA = rheumatoid arthritis; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SoA = schedule of assessments; WOCBP = woman of childbearing potential; WONCBP = woman of nonchildbearing potential.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor:

R-Pharm International

Name of Finished Product:

Olokizumab

Name of Active Ingredient:

Olokizumab

Protocol Title:

A Phase 1, Open-label, Study in Subjects with Rheumatoid Arthritis to Evaluate the Effect of a Single Dose of Olokizumab on the Pharmacokinetics of Substrates for CYP1A2, CYP2C9, CYP2C19, and CYP3A4

Protocol Number:

CL04041026

Rationale:

Olokizumab (OKZ) has been shown to reverse the inhibitory effect of IL-6 on the activity of Cytochrome P450 (CYP450) isozymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 in vitro.

To support the registration of OKZ, R-Pharm proposes a single-cocktail drug-drug interaction study design in subjects with rheumatoid arthritis (RA) to evaluate any potential effects of OKZ on the metabolism of substrates selective for specific CYP450 activity. The following probe substrates will be studied in the planned cocktail study: caffeine (CYP1A2), S-warfarin (CYP2C9), omeprazole (CYP2C19), and midazolam (CYP3A4).

Objectives and Criteria for Evaluation (Endpoints):

Objectives	Criteria for Evaluation (Endpoints)
Primary	
• To assess the effect of olokizumab (OKZ) on the pharmacokinetics (PK) of the Cytochrome P450 (CYP450) probe substrates, caffeine (CYP1A2), S-warfarin (CYP2C9), omeprazole (CYP2C19), and midazolam (CYP3A4) in subjects with rheumatoid arthritis	Primary • Area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{(0\text{-}inf)}$) for caffeine, omeprazole, and midazolam • AUC from time zero to the time "t" of the last quantifiable concentration ($AUC_{(0\text{-}last)}$) for S-warfarin • Maximum plasma concentration (C_{max}) for all cocktail substrates Secondary • Plasma $AUC_{(0\text{-}last)}$ or $AUC_{(0\text{-}inf)}$ (if not primary), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), elimination rate constant (λ_z), apparent systemic clearance (CL/F), and apparent volume of distribution (V_z/F) for cocktail parent compounds (caffeine, S-warfarin, omeprazole, and midazolam) • Plasma concentrations for OKZ

Secondary: Safety	
• To assess the safety and tolerability of the cocktail substrates when dosed in the presence or absence of OKZ • To assess the safety and tolerability of a single dose of OKZ in subjects with rheumatoid arthritis	• Assessment of adverse events (AEs), graded by Common Terminology Criteria for Adverse Events (CTCAE), physical examination, vital signs (blood pressure, pulse rate, and body temperature), standard 12-lead electrocardiogram (ECG), evaluation of laboratory parameters (clinical chemistry, hematology, and coagulation), and immunogenicity
Secondary: Pharmacodynamic	
• To assess the effect of OKZ on inflammatory markers (pharmacodynamics [PD]) in subjects with rheumatoid arthritis	• Interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations collected periodically throughout the study

Overall Design:

This is a Phase 1, open-label, 3-period, single-sequence, crossover study in subjects with RA with increased C-reactive protein (CRP) (≥1.2 × upper limit of normal [ULN]). During the study, subjects will be administered a cocktail of 4 substrates alone (Period 1) and in the presence of OKZ (Period 3). A single dose of 128 mg OKZ will be administered (Period 2) approximately 2 weeks prior to the second administration of the cocktail in Period 3. The cocktail comprises 100 mg caffeine (substrate of CYP1A2), 10 mg warfarin (containing 5 mg S-warfarin [substrate of CYP2C9]) plus 10 mg vitamin K, 20 mg omeprazole (substrate of CYP2C19), and 2 mg midazolam (substrate of CYP3A4) and will be administered after an overnight fast of at least 10 hours (Turpault et al, 2009). Serial blood samples will be collected to determine the PK of the cocktail substrate analytes and OKZ. Blood sampling for the measurement of IL-6 and CRP will also be performed.

Subjects will be screened within 35 days of the first dose administration and eligible subjects will be admitted to the study center on Day -1. The study will employ a 2-stage screening process; during the first Screening stage, assessments for genotyping, medical history with physical examination and FSH testing will be performed, as well as possibly the hepatitis serology and CRP screening assessments, if required by the study center. This will be followed approximately 3 weeks later by the second Screening stage, where the rest of the assessments will be conducted.

If a subject has a history of confirmed coronavirus disease 2019 (COVID-19) in the previous 3 months before Day 1 (or with sever or critical illness ever) or known exposure to an individual with confirmed COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within the past 2 weeks and it is revealed at the Screening Visit or prior to cocktail administration on Day 1, the subject should not be administered the study treatment, and further COVID-19 related testing is not required. In case a patient shows respiratory symptoms or informs the Investigator about contact with a COVID-19 infected person after OKZ administration, a test for COVID-19 should be performed as soon as possible.

It is estimated that 15 subjects who meet the study eligibility criteria will need to be dosed in order to achieve the required 12 evaluable subjects. However, if necessary, additional subjects may be dosed to obtain the 12 evaluable subjects required.

On the morning of Day 1 after an overnight fast of at least 10 hours, subjects will receive the first treatment of the cocktail: 100 mg caffeine, 20 mg omeprazole, 10 mg warfarin, 2 mg midazolam (via syringe) followed by 10 mg vitamin K (via syringe [Zhuang et al, 2015]), orally, under the supervision of appropriately trained study center staff. The cocktail will be administered with 240 mL of water and all 4 cocktail substrates as well as the vitamin K should be ingested within 5 minutes (for details regarding study treatment administration, see Section 6.1).

Subjects will remain in the study center until Day 2 and will be discharged at the Investigator's discretion (ie, providing there are no safety concerns) after the 30-hour PK sample. Subjects will return to the study center on Day 3, Day 4, Day 6, and Day 8 for PK sampling (see Table 4 for PK sampling times).

On completion of the 7-day PK sampling period for the cocktail substrates on the morning of Day 8, subjects will be administered a single subcutaneous (SC) dose of 128 mg OKZ. All subjects will remain at the study center for at least 2 hours after the injection to be assessed for any systemic hypersensitivity reactions. Blood samples for determination of OKZ concentrations will be collected on Day 8 (predose [30-minute window allowed], along with the final PK sample collection for warfarin), Day 9, and Day 15. Subjects will attend the study center on an outpatient basis on Day 8, Day 9, and Day 15.

Subjects will be admitted to the study center on Day 21 and will receive the second administration of the cocktail substrates after an overnight fast of at least 10 hours on Day 22 (ie, 14 days after administration of OKZ, by which time maximum suppression of CRP is expected). Subjects will remain in the study center until the 30-hour PK samples (caffeine) have been taken on Day 23 and will return to the study center on Day 24, Day 25, Day 27, and Day 29 (End of Treatment [EOT]) for scheduled PK sampling (warfarin) (see Table 4 for PK sampling times). Blood sampling for determination of OKZ concentrations will be collected on Day 22 (prior to cocktail administration) and on Day 24 and Day 29 (see Table 5 for PK sampling times).

The IL-6 and CRP levels will be measured at Screening, prior to dose administration with the cocktail substrates on Day 1, prior to administration with OKZ on Day 8, and post OKZ administration on Day 9, Day 15, Day 22 (prior to dose administration of the cocktail), and Day 29, which will be considered the EOT Visit. Safety assessments will be performed at the EOT Visit (Day 29).

Subjects will be undergoing COVID-19 reverse transcription polymerase chain reaction (RT-PCR) testing. Two RT-PCR tests will be conducted, the second RT-PCR test will only be performed if the first test results are negative. Only subjects with a negative COVID-19 RT-PCR test result may be included in the study. Two consecutive RT-PCR tests will occur at Day -35 (Stage 1) - only if the Investigator suspects possible COVID-19 infection, at Day -3, Day 5, Day 19 and Day 29 (EOT) - obligatory. If the Investigator suspects possible COVID-19 infection the RT-PCR testing should also occur on Day 43. Only subjects with a negative COVID-19 RT-PCR test result may be administered the study drug on Day 8. The RT-PCR testing will be performed at local laboratories.

A rapid test will be conducted for the COVID-19 immunoglobulin G (IgG)/immunoglobulin M (IgM) testing at Screening-Stage 1 - only if the Investigator suspects possible COVID-19 infection, prior to first inhouse period (Day -2) - obligatory. If the Investigator suspects possible COVID-19 infection, the IgG/IgM testing should also be performed prior to dose administration on Day 8 or/and prior to second inhouse period (Day 19) or/and Day 43. The serology will be performed onsite.

The Investigator's decision on COVID-19 infection should be based on patient's contacts, travels, presence or absence of any complaints, signs and symptoms suspicions for COVID-19 infection, local circumstance, or any other conditions if applicable.

The Safety Follow-up Visit on Day 99 ±7 days is scheduled at approximately 3 × OKZ terminal half-life ($t_{1/2}$). Subjects who discontinue the study early, should be asked to return for an EOT (Day 29) and Safety Follow-up Visit (Day 99) - with exception of the cases when it is not possible such as the cases with COVID-19 infection when the subject will come to the visit after recovery (subject should not be infectious at the time of EOT and follow-up visits). There will be 2 additional telephone follow-up calls, with the subject, on Day 130 ±7 days and Day 161 ±10 days (End of Study [EOS]) after the EOT, at approximately 4 × OKZ $t_{1/2}$ and 5 × OKZ $t_{1/2}$, respectively.

Number of Investigators and Study Centers:

Approximately 3 Investigators and study centers are expected to participate in this study.

Number of Subjects:

Twelve evaluable subjects will be required to complete this study. It is estimated that 15 subjects who meet the study eligibility criteria will need be dosed in order to achieve this number. However, if necessary, additional subjects may be dosed to obtain the 12 evaluable subjects required.

Treatment Groups and Duration:

Subjects with active RA and on a stable dose of methotrexate (MTX), as defined by the inclusion and exclusion criteria will be included in a single treatment group.

There will be a 35-day Screening Period, followed by a 29-day study duration and a 19-week (133-day) follow-up period. The duration of the study will be approximately 200 days (approximately 6 and a half months).

Study Treatments Administered:

- Olokizumab: Sterile solution for subcutaneous (SC) injection, 128 mg (0.8 mL injection), SC injection
- Caffeine: Tablet, 100 mg, oral
- Warfarin: Warfarin Tablet plus vitamin K solution for intravenous injection, 10 mg and 10 mg/mL (vitamin K), oral
- Omeprazole: Tablet, 20 mg, oral
- Midazolam: Syrup, 2 mg/mL, oral

Diagnosis and Main Criteria for Inclusion:

Eligible subjects must be willing and able to give informed consent and sign an Informed Consent Form (ICF) to be included in the study and were: male subjects or female subjects aged ≥18 to ≤70 years of age with a body mass index of 18 kg/m^2 to 29.9 kg/m^2, inclusive, and body weight of 55 kg to 110 kg, inclusive, if male, and 45 kg to 100 kg, inclusive, if female. Subjects must have a diagnosis of adult onset RA classified by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 revised classification criteria for RA (Aletaha et al, 2010) for at least 12 weeks prior to Screening. If the subject was diagnosed according to ACR 1987 criteria previously, the Investigator may classify the subject per ACR 2010 retrospectively, using available source data. Subjects must have received MTX, sulfasalazine, or hydroxychloroquine for at least 12 weeks prior to Day 1 and in stable dose for at least 6 weeks prior to Day 1 without significant AEs. Stable doses of MTX should be 10 mg to 25 mg weekly with folic acid (at least 5 mg weekly or equivalent). No significant side effects based on the Investigator's judgment should be observed during treatment by these agents. Male subjects and their female partners and female subjects of childbearing potential are to adhere to the contraceptive requirements for the study. See Appendix 6 for details regarding contraceptive requirements.

For details on exclusion criteria see Section 5.2.

Statistical Methods:

Calculation of Sample Size:

No historical data are available for the reduction in S-warfarin area under the plasma concentration-time curve from time zero extrapolated to the last quantifiable concentration ($AUC_{(0\text{-last})}$) following administration of OKZ. Hence, the following sample size computation is based on results reported for another compound (sirukumab) in the same class of medications as OKZ. Zhuang et al (2015), reported an 18% (90% confidence interval [CI]: 0.73 to 0.92), 18% (90% CI: 0.73 to 0.92), and 19% (90% CI: 0.72 to 0.91) reduction in S-warfarin $AUC_{(0\text{-inf})}$ at 1, 3, and 6 weeks, respectively, following sirukumab administration in 12 subjects with RA. Assuming a dropout rate of 20%, approximately 15 subjects who meet the study eligibility criteria should be enrolled so that 12 evaluable subjects complete the study. However, if necessary, additional subjects may be dosed to obtain the 12 evaluable subjects required. This sample size (ie, 12 evaluable subjects) will have over 95% power to determine whether a 90% CI of the S-warfarin $AUC_{(0\text{-last})}$ ratio of the geometric mean for some timepoint after the administration of OKZ to

that before OKZ administration is within the interval 80% to 125%. The power was calculated assuming a 13% coefficient of variation (CV) for S-warfarin $AUC_{(0\text{-last})}$.

Similarly, no historical data are available for the reduction in midazolam and omeprazole $AUC_{(0\text{-inf})}$ following administration of OKZ. Based on Zhuang et al (2015), a sample size of 12 subjects with RA was sufficient to describe the effect of sirukumab on the model substrates midazolam and omeprazole with a reduction in $AUC_{(0\text{-inf})}$ of 30% (90% CI: 0.51 to 0.96) to 35% (90% CI: 0.47 to 0.89) and 37% (90% CI: 0.36 to 1.09) to 45% (90% CI: 0.32 to 0.96), respectively, following sirukumab administration in 12 subjects with RA. Similarly, the effect of tocilizumab infusion on simvastatin and omeprazole exposure was well described with 8 subjects (28% reduction in omeprazole $AUC_{(0\text{-inf})}$) (Zhou and Meibohm, 2013). No statistical powering or formal comparisons are planned for midazolam and omeprazole substrates.

Caffeine is included in this study to further evaluate the effect of CYP450 modulators on this isozyme in subjects with RA. Again, no historical data are available for the reduction in caffeine $AUC_{(0\text{-inf})}$ following administration of OKZ. As per Zhuang et al (2015), caffeine $AUC_{(0\text{-inf})}$ was increased by 20% (90% CI: 0.75 to 1.91) to 34% (90% CI: 0.84 to 2.15) following sirukumab administration in 12 subjects with RA. This study is not powered to detect treatment differences in caffeine.

Analysis Sets:

The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment (cocktail or OKZ). Subjects will be analyzed according to the treatment they received.

The Pharmacokinetic (PK) Analysis Set will include all subjects who receive at least 1 dose of study treatment (cocktail or OKZ) and have at least 1 quantifiable plasma concentration for any of the cocktail substrates or OKZ collected postdose without protocol deviations or events that could affect those concentrations. The list of protocol deviations or events that could affect the plasma concentrations will be finalized before the database lock from the list of all protocol deviations that occurred during the study.

The Pharmacodynamic (PD) Analysis Set will include all subjects who receive at least 1 dose of study treatment (cocktail or OKZ) and who have at least 1 PD endpoint collected after cocktail or OKZ administration without protocol deviations or events that could affect those endpoints. The list of protocol deviations or events that could affect the PD endpoints will be finalized before the database lock from the list of all protocol deviations that occurred during the study.

Pharmacokinetic Analysis:

Concentrations and PK parameters for the cocktail drugs (caffeine, S-warfarin, omeprazole, and midazolam), and OKZ (concentration only) in plasma will be summarized using descriptive statistics.

The natural log transformed PK parameters (maximum concentration [C_{max}], $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-last})}$) of each cocktail substrate will be analyzed using a linear mixed effects model with a fixed effect for treatment and a random effect for subject. Estimates of the mean difference between treatments (OKZ + cocktail substrate compared to cocktail substrate alone) and its associated 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale to obtain estimates of the geometric mean ratios and the associated 90% CIs.

Interpretation of the results will be based on the size of the geometric mean ratios and associated 90% CIs.

Pharmacodynamic Analysis:

Interleukin-6 (IL-6) and CRP concentrations and their change from baseline (CFB) concentration values will be listed and summarized by scheduled collection time.

Safety Analysis:

All safety data will be listed and summarized including any AEs, AEs with an outcome of death, serious adverse events (SAEs), AEs leading to discontinuation of study treatment, 12-lead electrocardiogram (ECG), vital signs, physical examination results, and safety laboratory assessments. Treatment-emergent

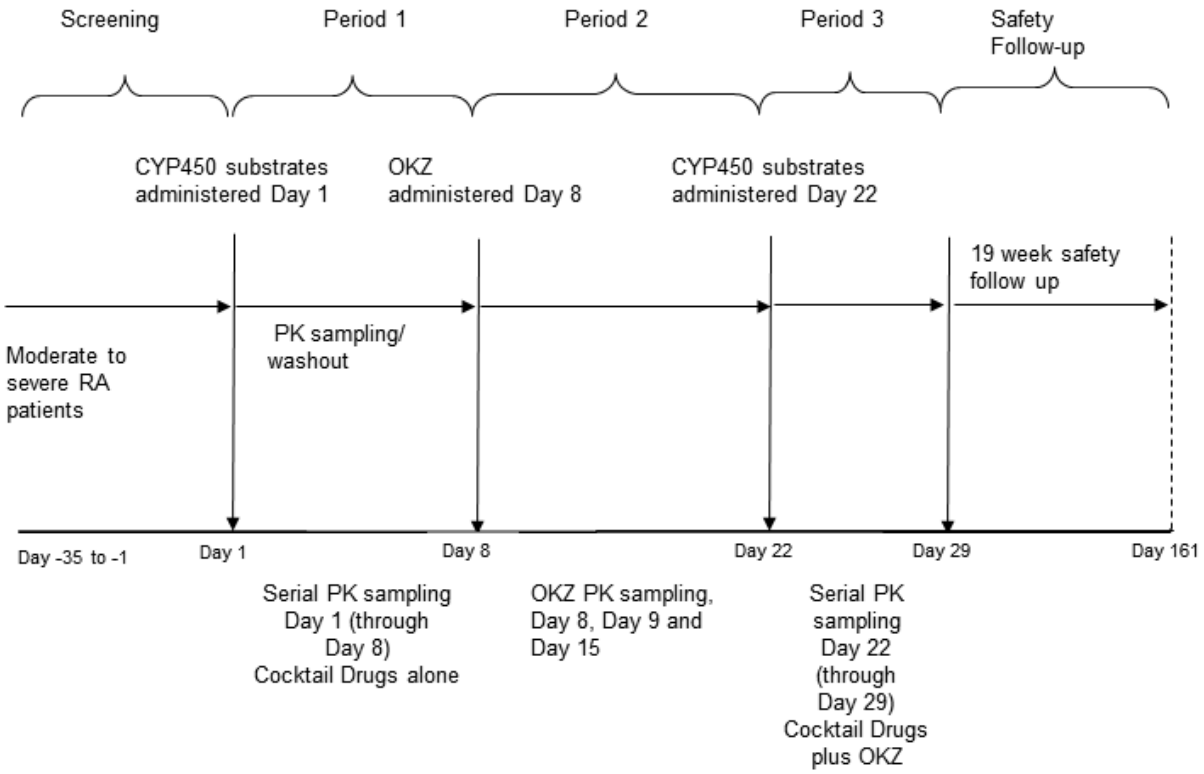
AEs (TEAEs) will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC). All AEs with an outcome of death, SAEs, and AEs leading to discontinuation of study treatment will be summarized similarly. TEAEs will be further summarized by relationship to study drug and severity.

The number and percentage of subjects testing positive for antidrug antibodies (ADAs) will be summarized over time.

Data Monitoring Committee: No

1.2 Schema

Figure 1 Study Schema



CYP450 = cytochrome P450; OKZ = olokizumab; PK = pharmacokinetic; RA = rheumatoid arthritis

1.3 Schedule of Activities

Table 3 Schedule of Activities

Assessments																									
Visit	**Scr[a]**			**3**			**4 to 7[b]**				**8**	**9**	**10**	**11**	**12**			**13 to 15[b]**			**16**	**17**	**18**	**19**	**20**
Day	**Stage 1 (V1)**	**Stage 2 (V2)**	**-3;-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**15**	**19**	**21**	**22**	**23**	**24**	**25**	**27**	**29 (EOT)**	**43**	**99 (SFU)**	**130**	**161 (EOS)**
Visit Window where applicable (days)	**-35 to -1**															**±1**					**+1**	**±3**	**±7**	**±7**	**±10**
Informed consent	X																								
Inpatient visits				X	X	X									X	X	X								
Outpatient visits	X	X	X				X	X	X	X	X	X	X	X				X	X	X	X		X		
Telephone follow-up																						X		X	X
CYP2C9, CYP2C19 and VKORC1 genotyping	X																								
Medical history and current medical conditions	X			X																					
Inclusion/exclusion criteria		X		X																					
Demography		X																							
Joint count (DAS28) and Patient Global Assessment of Disease Activity (Visual Analog Scale – Bullet Scale)					X[c]						X[c]										X				
Height		X																							

Assessments																								
Visit	**Scr[a]**			**3**			**4 to 7[b]**				**8**	**9**	**10**	**11**	**12**			**13 to 15[b]**			**16**	**17**	**18**	**19**	**20**
Day	**Stage 1 (V1)**	**Stage 2 (V2)**	**-3;-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**15**	**19**	**21**	**22**	**23**	**24**	**25**	**27**	**29 (EOT)**	**43**	**99 (SFU)**	**130**	**161 (EOS)**
Visit Window where applicable (days)	**-35 to -1**															**±1**					**+1**	**±3**	**±7**	**±7**	**±10**
Weight		X			X[c]						X[c]					X[c]					X				
Physical examination[d]	X	X	X	X							X[c]			X		X[c]					X	X	X		
Vital signs[e]		X		X							X[c]										X		X		
12-lead ECG		X		X							X[c]										X				
FSH[f]	X																								
Pregnancy test (blood)[g]		X																							
Pregnancy test (urine)[g]				X							X[c]				X						X		X		
TB risk questionnaire[h]		X																							
Chest radiography[i]		X																							
QuantiFERON-TB Gold Plus Assessment		X																							
HIV serology		X																							
HBsAg, anti-HBs, anti-HBc, HBV DNA, HCV Ab[j]	X	X																							
Drugs of abuse, cotinine, and alcohol screen		X		X							X[c]				X										

Assessments																									
Visit	**Scr[a]**			**3**			**4 to 7[b]**				**8**	**9**	**10**	**11**	**12**			**13 to 15[b]**			**16**	**17**	**18**	**19**	**20**
Day	**Stage 1 (V1)**	**Stage 2 (V2)**	**-3;-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**15**	**19**	**21**	**22**	**23**	**24**	**25**	**27**	**29 (EOT)**	**43**	**99 (SFU)**	**130**	**161 (EOS)**
Visit Window where applicable (days)	**-35 to -1**															**±1**					**+1**	**±3**	**±7**	**±7**	**±10**
HbA1c		X																							
Hematology[k]		X[l]									X[c]										X		X		
Chemistry panel[m]		X[l]									X[c]										X		X		
Urinalysis		X[l]																			X				
Coagulation panel[n]		X[l]		X							X[c]										X				
INR only[o]						X	X	X	X	X					X		X	X	X	X					
Blood sampling for PGx future testing					X[c]																				
Administer cocktail					X											X									
Administer OKZ											X[p,q]														
Assess injection site reactions[r]											X	X													
AEs/SAEs[s]	X	X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X		X	X	X
Concomitant and prior medications/nondrug therapy		X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X		X	X	X
IL-6/CRP samples	X[t]	X			X[c]						X[c]	X	X			X[c]					X				
Cocktail PK samples[u]					X	X	X	X		X	X					X	X	X	X	X	X				
OKZ PK samples[v]											X[c]	X	X			X[c]		X			X				
ADAs[w]											X[c]										X		X		

Assessments																									
Visit	**Scr[a]**			**3**			**4 to 7[b]**				**8**	**9**	**10**	**11**	**12**			**13 to 15[b]**			**16**	**17**	**18**	**19**	**20**
Day	**Stage 1 (V1)**	**Stage 2 (V2)**	**-3;-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**15**	**19**	**21**	**22**	**23**	**24**	**25**	**27**	**29 (EOT)**	**43**	**99 (SFU)**	**130**	**161 (EOS)**
Visit Window where applicable (days)	**-35 to -1**															**±1**					**+1**	**±3**	**±7**	**±7**	**±10**
COVID-19 RT-PCR testing[x,y]	X[bb]		X						X[z]					X							X[aa]	X[bb]			
COVID-19 IgM/IgG testing[cc]	X[bb]		X								X[bb]			X[bb]								X[bb]			

Abbreviations: Ab = antibody; ADA = antidrug antibody; AE = adverse event; ALT = alanine aminotransferase; anti-HBs = hepatitis B surface antibody; anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; CK = creatine kinase; COVID-19 = Coronavirus disease 2019; CRP = C-reactive protein; CYP = Cytochrome P450; DAS28 = Disease Activity Score 28 joint count; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FSH = follicle-stimulating hormone; GGT = gamma glutamyl transpeptidase; HbA1c = glycosylated hemoglobin A_{1c}; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; ICF = Informed Consent Form; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IL-6 = interleukin-6; INR = international normalized ratio; OKZ = olokizumab; PK = pharmacokinetic; RBC = red blood cells; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; Scr = screening; SFU = safety follow-up; TB = tuberculosis; V = visit; VKORC1 = Vitamin K epOxide Reductase Complex subunit 1; WBC = white blood cells. WOCBP = woman of childbearing potential; WONCBP = woman of nonchildbearing potential.

[a] The study will employ a 2-stage screening process; during the first Screening stage, assessments for genotyping, medical history with physical examination and FSH testing will be taken, followed approximately 3 weeks later by the second Screening stage, when the rest of the assessments will be conducted. The second Screening stage should not be initiated until eligibility has been confirmed during the first Screening stage. If needed, assessments can be performed on multiple days during the Screening stages.

[b] Outpatient visits; optional inpatient stay at the discretion of Investigator and subject.

[c] Predose relative to the scheduled treatment.

[d] A complete physical examination will be performed at scheduled timepoints, and as needed (see Section 8.1.1). Physical examinations include but are not limited to respiratory infection symptoms (acute onset of cough, fever [oral temperature >37.5°C], dyspnea) and asked about contacts with suspected or confirmed COVID-19 cases/visiting areas where high frequency of COVID-19 are reported.

[e] Vital signs include temperature, pulse rate, and BP. At Screening, BP should be done in triplicate and the mean used to assess for subject eligibility. Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 BP measurement. In addition, BP and pulse also need to be reassessed 1 and 2 hours following OKZ administration on Day 8 (See Section 8.1.2).

[f] Levels of FSH to be assessed in female subjects presenting as postmenopausal to determine they are of in fact postmenopausal. For inclusion into the study as WONCBP the FSH level at Screening should be ≥40 mIU/mL.

[g] Performed for female subjects considered as WOCBP.

[h] The questionnaire "Tuberculosis Risk Questionnaire" (see Appendix 8) should be used as a source document. At the Screening Visit, if question No. 1 (Does the subject have currently active TB disease or a history of active TB disease) or question No. 2 (Has the subject been in close contact [ie, sharing the same household, or other enclosed environment, such as a social gathering place, workplace, or facility, for extended periods during the day] with an individual with active TB within the past 1.5 years) of the questionnaire "Tuberculosis Risk Questionnaire for Screening Visit" is answered "Yes" the subject is not allowed to enter the study (see exclusion criterion No. 23, Section 5.2). 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.

[i] Chest radiography (both posteroanterior and lateral) need not be conducted if performed within 8 weeks prior to the date of Screening and films are available for review. Films available at Screening or collected at Screening should be kept as source documents.

[j] Hepatitis serology testing could be done during first stage of screening if required by the study center. HBV DNA to be tested in anti-HBc positive subjects only.

[k] Hematology includes RBC, WBC with differential, hemoglobin, hematocrit, and platelet count (see Appendix 3 for details).

[l] For subjects with abnormal laboratory values at Screening, 1 retest is allowed at the Investigator's discretion within the 35-day Screening period to assess eligibility (see Section 8.1.4).

[m] The chemistry panel includes creatinine, fasting glucose, sodium, potassium, total protein, total bilirubin, direct, and indirect bilirubin, ALT, AST, alkaline phosphatase, GGT, creatine kinase, albumin, and total cholesterol (see Appendix 3 for details).

[n] Samples for the coagulation panel (INR, aPTT, and fibrinogen) should be collected prior to all other blood samples (see Appendix 3).

[o] INR results should be available within 24 hours (and for the sample taken on Day 21, before cocktail administration on Day 22).

[p] OKZ should be administered after the final S-warfarin blood sample is obtained on Day 8. Subjects will remain at the study center for at least 2 hours after the injection of OKZ to be assessed for onset of any systemic hypersensitivity reactions.

[q] Only patients with a negative COVID-19 RT-PCR result may be administered the study drug.

[r] Prior to and following OKZ administration. Additional injection site assessments may be performed at the Investigator's discretion.

[s] Serious AEs and AEs are reported from the signature of the ICF.

[t] The CRP test to assess eligibility can be done during the first stage of Screening and can be repeated once during Screening, provided results arrive prior to the admission date. No extensions of the Screening period will be granted for missing laboratory data unless this is due to central laboratory error (after Sponsor approval).

[u] See Table 4 for times of blood collection for the various cocktail substrates.

[v] See Table 5 for times of blood collection for OKZ.

[w] Neutralizing antibodies will be tested in samples that were positive for OKZ antibodies.

[x] COVID-19 RT-PCR testing: two RT-PCR tests should be performed within approximately 36 hours (a second RT-PCR would be performed only if the first results are negative).

[y] Sample may be taken at the local laboratory or another designated sample collection area.

[z] Results for the RT-PCR tests should be available before OKZ is administered on Day 8 (a second RT-PCR would be performed only if the first results are negative).

[aa] If a subject is withdrawn from the study due to COVID-19 and returns for the EOT Visit after recovery, out of study positive RT-PCR results will be acceptable, it is not necessary to repeat a negative RT-PCR test if the subject is considered recovered from COVID-19 by the local guidelines.

[bb] Only if the Investigator suspects possible COVID-19 infection.
[cc] Using rapid test.

Table 4 Times of Blood Collection for the Cocktail Substrates

Day	Day	Time (hours postdose)	Midazolam	Omeprazole[b]	Caffeine[b]	S-Warfarin[b]
1	22	Predose[a]	1	1	1	1
1	22	0.25 (± 2 min)	1	1	1	1
1	22	0.5 (± 2 min)	1	1	1	1
1	22	1 (± 5 min)	1	1	1	1
1	22	1.5 (± 5 min)	1	1	1	1
1	22	2 (± 5 min)	1	1	1	1
1	22	3 (± 5 min)	1	1	1	1
1	22	4 (± 5 min)	1	1	1	1
1	22	6 (± 5 min)	1	1	1	1
1	22	8 (± 5 min)	1	1	1	1
1	22	12 (± 5 min)	1	1	1	1
2	23	24 (± 5 min)	1	1	1	1
2	23	30 (± 5 min)			1	
3	24	48 (± 2 hr)				1
4	25	72 (± 2 hr)				1
6	27	120 (± 2 hr)				1
8	29	168 (+1 day)				1

[a] Predose blood samples for cocktail substrates should be taken within 30-minutes prior to the administration of the cocktail substrates.

[b] A single blood sample or separate samples may be taken at shared timepoints.

Table 5 Times of Blood Collection for OKZ

	Time		
Day	**Predose**	**Postdose**	**OKZ**
8[a]	Within 30-minutes		1
9		Should be clock-matched to the sample on Day 8	1
15		Should be clock-matched to the sample on Day 8	1
22		Should be collected prior to the administration of the cocktail substrates	1
24		Should be clock-matched to the sample on Day 22	1
29[b]		Should be clock-matched to the sample on Day 22	1

[a] Sample collected on Day 8 should be collected within 30 min prior to OKZ administration.

[b] A window of +1 day is allowed for this visit.

2.0 INTRODUCTION

2.1 Study Rationale

Olokizumab (OKZ) is being developed by R-Pharm International for the treatment of moderately to severely active rheumatoid arthritis (RA). Olokizumab is a humanized (complementarity determining region [CDR] grafted) monoclonal antibody (mAb) of immunoglobulin (Ig) G4/kappa isotype, developed as an antagonist of interleukin-6 (IL-6) that is anticipated to have utility in a wide range of autoimmune/inflammatory conditions.

As a consequence of co-morbidities, patients with RA, may require treatment with many medications which undergo metabolism through Cytochrome P450 (CYP450) enzymes and due to ongoing inflammation, they often have elevated cytokine levels including IL-6 in synovial fluid (Arend et al, 1990) and in the systemic circulation. In in vitro models, IL-6 has been found to suppress the activity of CYP450 enzymes (such as CYP3A, CYP2C19, CYP2C9, and CYP1A2) (Abdel Razzak et al, 1993) leading to reduced metabolism and therefore higher exposure to CYP450 substrates (Lee et al, 2010).

It is hypothesized that drugs such as OKZ, which reduce levels of cytokines or inhibit cytokine signaling pathways, may reverse cytokine mediated suppression of CYP450s in patients with RA, resulting in normalization of CYP450 substrate plasma levels. For example the anti-IL-6 mAb tocilizumab has been shown to normalize IL-6 induced suppression of CYP450s in vitro (Tocilizumab SPC, 2016) and to reduce the plasma levels of omeprazole and simvastatin (CYP2C19 and CYP3A substrates, respectively) in patients with RA compared to values prior to tocilizumab treatment. Similarly, the anti-IL-6 mAb sirukumab, reversed IL-6 mediated suppression of CYP3A, CYP2C19 and CYP2C9 in a cocktail study performed in patients with RA (Zhuang et al, 2015).

The primary objective of the current study is to evaluate the effects of a single subcutaneous (SC) 128 mg injection of OKZ on the pharmacokinetics (PK) of the probe CYP450 substrates midazolam (CYP3A), omeprazole (CYP2C19), S-warfarin (CYP2C9) and caffeine (CYP1A2), in subjects with active RA.

The subjects to be included in this study must have raised CRP levels (≥1.2 × upper limit of normal [ULN]) indicating active inflammation, which is necessary for the adequate characterization of the drug-drug interaction potential of OKZ.

2.2 Background

Rheumatoid arthritis is an 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 lead to significant morbidity, and accelerated mortality (Jacobsson et al, 2007). Moderate to

severe RA is often treated with disease modifying antirheumatic drugs (DMARDs), with methotrexate (MTX) being the most commonly used. For patients with an inadequate response to conventional DMARDs, biologic agents which inhibit tumor necrosis factor alpha (TNF-α), especially in combination with MTX, are indicated (Smolen et al, 2014). Nonetheless, a substantial proportion of patients receiving biologics (ie, approximately 40% to 50% of those receiving TNF-α inhibitor [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.

The inflammation as well as the emergence of disease-specific autoantibodies, and the characteristic acute phase response in RA may be explained, at least in part, by observed sustained IL-6 overproduction (Yoshizaki et al, 1998). Tocilizumab (TCZ), known as RoActemra® or Actemra®, a recombinant humanized mAb that acts as an IL-6R antagonist, has been approved for the treatment of moderate to severe RA (Tocilizumab SPC, 2016).

According to the Actemra prescribing information, the following warnings exist, and precautions should be taken:

- Serious Infections – do not administer Actemra during an active infection, including localized infections. If a serious infection develops, interrupt Actemra until the infection is controlled.
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk.
- Laboratory monitoring – recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests.
- Hypersensitivity reactions, including anaphylaxis, and death have occurred.
- Live vaccines – Avoid use with Actemra.

Targeting the IL-6 pathway, either via IL-6R, or the cytokine itself, may provide a favorable risk-benefit profile for the treatment of a potential number of other human diseases besides RA.

Anti-IL-6 agents offer the possibility of broad-spectrum activity across the immune mediated disease spectrum. Within the class of therapeutic antibodies targeting the IL-6 pathway, OKZ is anticipated to be potentially more potent because of its high affinity for IL-6 and its axis of intervention (inhibiting the interaction between IL-6 and signal transducing receptor gp130). Also, as OKZ is of the IgG4 isotype, it would not be expected to mediate significant levels of antibody-mediated complement fixation or cell-mediated cytotoxicity.

2.2.1 Nonclinical Data

Olokizumab has been shown to have a high affinity for human IL-6 as determined by BIAcore analysis, with a corresponding dissociation constant of approximately 10 pM. Additionally, in vitro whole blood and cell line assays were also performed to assess the effect of OKZ on IL-6

signaling. Results showed that OKZ potently neutralizes IL-6-mediated effects in vitro, and no evidence was found that OKZ could mediate activation of the IL-6 signaling pathway.

The PK of OKZ has been investigated in the cynomolgus monkey following either a single intravenous (IV) (1 and 10 mg/kg) or single SC (10 mg/kg) administration. Peak plasma levels of OKZ after an IV administration, infused over 2 minutes, occurred after 5 minutes and for SC administration, it occurred after 2 to 4 days. Plasma levels of OKZ decreased slowly after dose administration with a $t_{1/2}$ of approximately 10 to 11 days. The bioavailability of OKZ after SC administration was shown to be approximately 80% compared to IV administration.

Antibodies to OKZ were detected in monkeys after a single dose of 1 mg/kg IV or 10 mg/kg SC. However, no detectable levels of antibodies to OKZ were found in any plasma samples from animals receiving >10 mg/kg IV or 50 mg/kg SC. As the presence of OKZ in all postdose samples could have interfered with detection of antibodies, these results should be interpreted with caution.

The pharmacodynamic (PD) properties of OKZ were assessed in both mice and cynomolgus monkeys. In mice, an acute phase response (measured as release of serum amyloid A [SAA]) induced by injection of human IL-6 was inhibited by OKZ in a dose-related manner with maximal inhibition noted at 0.3 mg/kg ($p < 0.001$).

General toxicology studies have shown that inhibition of IL-6 signaling does not result in any adverse effects either in animal models or formal toxicology studies. Olokizumab is well tolerated in the cynomolgus monkey. No target organ toxicity was noted, however, decreases in haptoglobin and fibrinogen levels were observed consistently for animals treated with OKZ. These are considered to be pharmacologically related since both haptoglobin and fibrinogen are acute phase proteins under the control of IL-6 (Akira et al, 1993). Despite very high doses of OKZ, far above those required for full target neutralization, the decrease in fibrinogen levels plateaued and did not interfere with coagulation and did not result in bleeding events. Decreases are also expected in humans, although to a lower extent and are not expected to interfere with coagulation.

No deaths or early termination of OKZ-treated animals were noted in the 13/26-week toxicity study (doses of 20 to 200 mg/kg/week SC). Olokizumab-related effects were limited to slight reductions in haptoglobin and fibrinogen, slightly lower numbers of immune cells, evidence of decreased/delayed antibody production in response to antigen challenge, and higher thymus weight, all of which could be related to the pharmacology of IL-6. These changes were not associated with an increased rate of infection or impaired coagulation/apparent bleeding events. Full reversibility was not observed for all parameters by the end of the 26-week treatment-free period, possibly due to remaining plasma OKZ.

In the prenatal and postnatal development in the cynomolgus monkey, the animals were well exposed, the treatment was well tolerated during pregnancy, and had no abortifacient effect.

Mortality was observed at delivery in some OKZ-treated maternal animals, without premonitory signs, and in some infants of OKZ-treated animals.

The local tolerance after IV and SC administrations of OKZ was also assessed as part of the repeat-dose studies in the cynomolgus monkey. No macroscopic or histological changes were observed at the infusion or injection sites. An acute SC local tolerance study in rats comparing 4 formulations at 2 dose levels was conducted and all injections were well tolerated.

Olokizumab is not expected to induce drug-drug interactions. Nevertheless, as IL-6 has been shown to downregulate the expression and to decrease the activity of some CYP450 enzymes involved in the metabolism of drugs, the possibility cannot be ruled out that treatment with OKZ may change the metabolism rate of CYP450-metabolized drugs to levels observed in control conditions. A study has been conducted to evaluate the effects of OKZ on CYP450 enzymes in vitro (Study Number NCD2107). Data indicate that, in cryopreserved human hepatocytes, IL-6 treatment for 48 hours resulted in a down-regulation of the activity of CYP1A1/2, CYP2B6, CYP2C9, CYP3A4/5, and CYP2C19 and the activity of sodium/taurocholate cotransporting polypeptide (NTCP). The activity of CYP2D6, organic cation transporting polypeptides (OCTPs) and organic anion transporting polypeptides (OATPs) was not affected. Olokizumab had no effects on the activity of CYP450 enzymes or the transporters NTCP, OCTPs, or OATPs. In contrast, OKZ reverses the inhibitory effect of IL-6 on the activity of CYP1A1/2, CYP2B6, CYP2C9, CYP3A4/5, and CYP2C19, and on the activity of NTCP.

Taken together, the nonclinical data were deemed sufficient to support the clinical development of OKZ in humans for the treatment of moderate to severe RA, other autoimmune inflammatory diseases, and oncological diseases with IL-6 pathophysiology.

2.2.2 Clinical Data

Eleven clinical studies with OKZ have been completed and include:

- two Phase 1 studies (Study RA0001 in 67 male healthy volunteers [Kretsos et al 2014] and RA0074 in 20 male Japanese healthy volunteers);
- a Phase 1/2a study (Study RA0010) in 40 subjects (7 males and 33 females) with RA and relatively low disease activity on stable doses of MTX;
- a Phase 2 study (Study RA0056 [Genovese et al, 2014]) in 221 subjects (33 males and 186 females) with active RA who had previously failed TNFi therapy;
- a Phase 2b open-label extension (OLE) study to Study RA0056 (Study RA0057) in 190 subjects (29 males and 161 females);
- a Phase 2 study (Study RA0083 [Takeuchi et al, 2016]) in 119 Asian subjects (16 males and 103 females) with active RA who had previously failed TNFi therapy; and

- a Phase 2 OLE study to Study RA0083 (Study RA0089) in 103 subjects (15 males and 88 females);
- a Phase 3 study (Study CL04041022) in 428 subjects (74 males and 354 females) with moderate to severe active RA inadequately controlled by MTX therapy (randomized to receive OKZ in two regimens or placebo);
- a Phase 3 study (Study CL04041023) in 1648 subjects (365 males and 1283 females) with moderate to severe active RA inadequately controlled by MTX therapy (randomized to receive OKZ in two regimens, adalimumab or placebo);
- a Phase 3 study (Study CL04041025) in 368 subjects with moderate to severe active RA inadequately controlled by TNFi therapy;
- a Phase 2/3 study (CL04041078) in subjects with severe SARS-CoV-2 virus infection (COVID-19).

Pharmacokinetic bioavailability of OKZ via SC administration was estimated to be 63% across the 3 studies evaluated (Studies RA0056, RA0001, and RA0010). The estimated $t_{1/2}$ in Study RA0001 and Study RA0010 was 31 days (median). Similar PK was observed in Study RA0056. In CL04041022, a steady state was reached by Week 16 and Week 14 for 64 mg OKZ administered once every 4 weeks (q4w) and once every 2 weeks (q2w), respectively. Accumulation based on the geometric means ratio for $AUC_{(0\text{-tau})}$ was 2.94-fold for q4w dosing and 3.52-fold for q2w dosing, consistent with the anticipated 1 month OKZ elimination half-life. Overall, across treatment groups, comparing average OKZ trough levels following q4w administration were approximately half those observed after q2w dosing. In CL04041023, mean OKZ trough concentrations, compared to the OKZ 64 mg q4w regimen, were 2.3- to 2.5-fold higher when OKZ was dosed q2w. In CL02021025, mean OKZ trough concentrations compared to the q4w regimen were 2.6- to 2.9-fold higher when OKZ 64 mg was dosed q2w. On graphical assessment for both CL04041023 and CL04041025 studies, steady-state appeared to be reached by 20 weeks post first dose in both treatment regimens. In study CL04041023, mean trough concentrations were up to 64% and 25% lower in the presence of ADAs for the q4w and q2w dosing regimens, respectively. In study CL04041025, mean trough concentrations were up to 21% and 32% lower in the presence of ADAs assessed across timepoints for the q4w and q2w dosing regimens, respectively.

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 serious adverse events (SAEs) (exacerbation of RA and Bowen's disease) in Study RA0010. One subject in Study RA0010, prematurely discontinued the study due to an AE (exacerbation of RA symptoms), but no subjects withdrew from Studies RA0001 or RA0074 due to treatment-emergent AEs (TEAEs).

In Study RA0056, OKZ was tolerated at doses of up to 240 mg every 2 weeks (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 prematurely discontinued from the study due to TEAEs (10 subjects in the OKZ groups and 1 subject in the placebo group).

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 1 subject each in the 60 mg (3.1%) and 240 mg (3.8%) OKZ groups. Overall, 2 subjects in the placebo group and 5 subjects in the OKZ groups reported a total of 9 TEAEs leading to premature discontinuation from the study.

The Phase 2 open-label extension studies (Studies RA0057 and RA0089) collected additional data on the safety of OKZ in subjects with RA over a 48-week treatment period. In Study RA0057, SAEs were reported by 50 subjects (26.3%). Overall, 33 subjects reported a total of 321 TEAEs leading to discontinuation. Three additional subjects reported AEs leading to permanent discontinuation of OKZ (bladder cancer, palmar pustular dermatitis, and cholecystis chronic). There were 2 deaths in this study (road traffic accident; necrotizing fasciitis (NF), acute renal failure, multi-system organ failure, and sepsis). In Study RA0089, SAEs were reported by 14 subjects (13.6%). Overall, 7 subjects reported a total of 33 TEAEs leading to discontinuation. There were no deaths in this study.

In CL04041022, OKZ was well tolerated at 64 mg q4w and 64 mg q2w doses. There was 1 death in this study (toxic shock syndrome) in OKZ q2w group. Less than 5% of subjects reported a SAE (mainly ALT increased, AST increased, rheumatoid arthritis, and subcutaneous abscess). Overall, 13 subjects (3.0%) reported at least 1 TEAE leading to discontinuation of study treatment; and 9 subjects (2.1%) reported at least 1 TEAE leading to withdrawal from the study.

In CL04041023, OKZ was well tolerated at 64 mg q4w and 64 mg q2w doses. A total of 80 (4.9%) subjects reported at least one treatment-emergent SAEs, with similar proportions of subjects with SAEs reported for the OKZ, adalimumab and placebo treatment groups. The most frequently reported SAEs were pneumonia (8 subjects [0.5%]), alanine aminotransferase increased (4 subjects [0.2%]), sepsis and urosepsis (4 subjects [0.2%]), and transaminases increased and hepatotoxicity (3 subjects [0.2%]). Seven subjects (0.4%) had a TEAE leading to death, and the incidences of death were comparable for the OKZ and placebo treatment groups. A total of 86 subjects (5.2%) reported at least 1 TEAE leading to discontinuation of study treatment; the most frequently reported TEAEs leading to withdrawal of study treatment were alanine aminotransferase increased, overall and transferases increased. Of the adverse events of special interest, Infections were reported for 534 subjects (32.5% of the safety population) overall, with similar proportions in each of the treatment groups.

In CL04041025, OKZ was well tolerated at 64 mg q2w and 64 mg q4w doses. A total of 18 subjects (4.9%) reported at least 1 treatment-emergent SAE and no TEAEs leading to death were

reported. Treatment emergent SAEs were reported for 6 subjects (3.2%) in the any OKZ q4w group, 12 subjects (7.0%) in the any OKZ q2w group, and no subjects (0.0%) in the placebo group. The frequency and type of SAE reported for the OKZ treatment groups were consistent with the SAEs reported for other OKZ clinical studies. A total of 18 subjects (4.9%) reported TEAEs leading to discontinuation of the study treatment. Overall, 15 subjects (4.1%) reported TEAEs leading to discontinuation from the study. The most frequently reported TEAEs leading to withdrawal of study treatment by SOC were Infections and infestations, reported for 6 subjects (1.6%) overall and Investigations, reported for 6 subjects (1.6%) overall.

In CL04041078, OKZ was well tolerated; the observed OKZ safety profile was consistent with the profile established in previous clinical studies and there were no new findings regarding the safety profile of OKZ. The occurrence of TEAEs was 35.5% in the OKZ group. Among them, 8.1% events were Grade 4 and 5. TEAEs related to the study drug were reported in 14.5% subjects in the OKZ group. TEAEs leading to discontinuation from the study were reported in 10 subjects (8.1%) in the OKZ group. At least 1 treatment-emergent SAE occurred in 8.1% subjects in the OKZ group in this study. Among them, 8.1% events in the OKZ group were Grade 4 and 5. Treatment emergent SAEs leading to death were reported in 7.3% subjects in the OKZ group.

Preliminary efficacy data in terms of 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, ie, 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.

In Study RA0056, a greater improvement in least squares (LS) mean DAS28 (CRP) from baseline at Week 12 was observed across all OKZ dose 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, every 4 weeks [q4w] and q2w dosing frequencies) was highly 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.

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 240 mg OKZ 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 dose group versus placebo ($p < 0.0001$ for each dose group). The comparisons of dosing frequency (120 mg OKZ group [60 mg q2w versus 120 mg q4w] and 240 mg OKZ [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 Phase 2 open-label extension study to Study RA0056 (Study RA0057) collected additional data on the efficacy of OKZ with respect to signs and symptoms of RA. All treatment groups from Study RA0056 were transferred to a single treatment group of 120 mg q2w in Study RA0057, and efficacy was assessed at Week 12, Week 24, and Week 48. Relative to Study RA0057 baseline, all treatment groups (with the exception of OKZ 60 mg q4w at Week 12), showed a decrease in DAS28 (CRP) at Week 12, Week 24, and Week 48. Subjects switching from the placebo group showed a marked improvement in DAS28 (CRP), similar to the improvement shown by subjects in the OKZ groups in the parent RA0056 study.

The Phase 2 open-label extension study to Study RA0083 (Study RA0089) in Japan, the Republic of Korea, and Taiwan collected additional data on efficacy in subjects with active RA. All treatment groups from Study RA0083 were transferred to a single treatment group of 120 mg q2w in Study RA0089, and efficacy was assessed at Week 12, Week 24, and Week 48. Relative to Week 0 of RA0083, there was a notable decrease in DAS28 (CRP) at Week 12, Week 24, and Week 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.

Confirmatory efficacy data were obtained in CL04041022 in subjects with moderately to severely active RA inadequately controlled by MTX. The ACR20 response was achieved at Week 12 by 191 subjects (100 subjects [70.4%] in the OKZ q4w group and 91 subjects [63.6%] in the OKZ q2w group) in OKZ group and 37 subjects (25.9%) in the placebo group. The secondary efficacy endpoint of DAS28 (CRP) < 3.2 response was achieved at Week 12 by 103 subjects (55 subjects [38.7%] in the OKZ q4w group and 48 subjects [33.6%] in the OKZ q2w group) in OKZ group and 5 subjects (3.5%) in placebo group.

In CL04041023 study in subjects with moderately to severely active RA inadequately controlled by MTX the ACR20 response was achieved at Week 12 by 342 subjects (71.4%) of 479 subjects in the OKZ q4w group, 326 subjects (70.6%) of 464 subjects in the OKZ q2w group and 108 subjects (44.4%) of 243 subjects in the placebo group. The DAS28 (CRP) < 3.2 score was achieved at Week 12 by 219 subjects (45.7%) in the OKZ q4w group, 210 subjects (45.3%) in the OKZ q2w group and 31 subjects (12.8%) in the placebo group.

In CL04041025 study in subjects with moderately to severely active RA inadequately controlled by TNF-α inhibitory therapy the ACR20 response was achieved at Week 12 by 96 subjects (59.6%) of 161 subjects in the OKZ q4w group, 84 subjects (60.9%) of 138 subjects in the OKZ q2w group, and 28 subjects (40.6%) of 69 subjects in the placebo group. The DAS28 (CRP) < 3.2 score was reported at Week 12 for 45 subjects (28.0%) in the olokizumab q4w group, 55 subjects (39.9%) in the olokizumab q2w group, and 8 subjects (11.6%) in the placebo group.

In CL04041078 in subjects with severe COVID-19 infection, primary efficacy results did not find the significant difference between treatment groups: there were 98 subjects (79.0%) of 124 subjects in the OKZ group classified as responders. The OKZ/placebo RR was 1.125 (one-

sided 97.5% CI: 0.989; ∞) (adjusted p=0.073). Analysis of secondary endpoints as well as exploratory endpoints also did not show the clinically significant difference in term of clinical outcomes and biomarkers levels. Mortality by Day 29 was 7.3% subjects in the OKZ group and 4.8% subjects in the placebo group. Relative risk for mortality: OKZ group/placebo group – 1.50 (two-sided 95% CI: 0.55; 4.09). Based on the study results it was concluded that OKZ does not contribute to improving the clinical status (relative to the respiratory system function) or mortality rates in patients with severe COVID-19, however, the potential benefit in relation to other clinical outcomes requires elucidation in further clinical studies.

A Phase 3 OLE study (Study CL04041024) in subjects with active RA previously completed CL04041022, CL04041023 or CL04041025 study are currently ongoing. According to the interim analysis of this study data OKZ is well tolerated at 64 mg q4w and 64 mg q2w doses. As of interim data cut-off date, there were 11 subjects (0.6%) that had a TEAE leading to death. The incidence rate was similar in all treatment sequence groups: 6 receiving the OKZ 64 mg q4w regimen and 5 receiving the OKZ 64 mg q2w regimen. One subject had a TEAE leading to death (completed suicide) that was assessed as related to study treatment by the Investigator; this subject had received adalimumab during the CL04041023 study followed by OLE OKZ 64 mg q4w. A total of 149 subjects (8.3%) reported at least 1 treatment-emergent SAE; 75 subjects (8.6%) in the OKZ q4w OLE group and 74 subjects (8.1%) in the OKZq2w OLE group. The most frequently reported SAEs by preferred term were ALT increased, reported for 9 subjects (0.5%), pneumonia reported for 8 subjects (0.4%), and cellulitis reported for 7 subjects (0.4%), and osteoarthritis reported for 6 subjects (0.3%). Confirmatory efficacy data derived by interim analysis shows the ACR20 response achievement at Week 52 by 341 subjects (148 subjects [16.7%] of 887 subjects in the OKZ q4w group and 193 subjects [21.5%] of 898 subjects in the OKZ q2w group) of total 1785 subjects in OKZ group. The DAS28 (CRP) < 3.2 response was achieved at Week 52 by 1153 subjects (575 subjects [64.8%] of 887 subjects in the OKZ q4w group and 578 subjects [64.4%] of 898 subjects in the OKZ q2w group) of total 1785 subjects in olokizumab group.

One more Phase 3 open-label randomized, comparative, parallel group, active controlled study in patients with moderate coronavirus infection (CL040401094) are currently ongoing.

The Phase 3 studies program includes efficacy and safety evaluations designed to demonstrate that OKZ can be used in a wide range of autoimmune/inflammatory conditions and to support marketing approval.

2.2.3 Pharmacokinetic Drug Interactions

Drug interactions with OKZ have not been investigated in clinical studies.

Hepatic CYP450 enzyme expression is known to be suppressed by IL-6 overproduction in subjects with inflammatory conditions (Aitken and Morgan, 2007; Carcillo et al, 2003; Frye et al, 2002). In vitro studies demonstrated that OKZ dose-dependently reversed IL-6-induced

suppression of the activities of the assayed CYP450 enzymes (ie, CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5) and of the bile acid transporter NTCP (see Section 5.2.4 of the IB). These findings suggest OKZ, via antagonism of IL-6, may restore the normal constitutive expression (and activity) of CYP450s and NTCP which had been previously suppressed in subjects with RA. As such, OKZ treatment may lead to a change in the systemic concentration and/or effect of coadministered drugs which are metabolized via the CYP450 enzymes and/or NTCP. These drugs include, but are not limited to, certain 'statins' (ie, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), calcium channel blockers, oral contraceptives, benzodiazepines, as well as theophylline, warfarin, phenytoin, and cyclosporine. Accordingly, while a subject is on OKZ treatment, close attention should be paid to the effectiveness or toxicity of their coadministered medication(s) known to be metabolized/eliminated by CYP1A1/2, CYP2B6, CYP2C9, CYP2C19, CYP3A4/5, and NTCP, and dose adjustments of concomitant medication(s) might be needed. Given the long elimination $t_{1/2}$ of OKZ, any such effects of OKZ on the expression of metabolizing enzymes and NTCP may persist for up to 4 months after the last administration of OKZ or until IL-6 concentrations become elevated.

This Phase 1, open-label drug-drug interaction study is planned to assess the effect of OKZ on the PK of substrates for CYP1A2, CYP2C9, CYP2C19, and CYP3A4 in subjects with RA.

2.3 Benefit/Risk Assessment

Olokizumab has undergone extensive nonclinical testing, and 11 clinical studies have been completed. In the difficult-to-treat population of subjects with RA who previously failed TNFi therapy, OKZ has demonstrated efficacy in 2 Phase 2 studies (Study RA0056 [extended with Study RA0057] in 221 subjects and Study RA0083 [extended with Study RA0089] in 119 Asian subjects). The efficacy of OKZ was further confirmed in subject population with moderate to severe active RA inadequately controlled by MTX therapy in CL04041022 (428 subjects) and CL04041023 (1648 subjects) studies as well as in 368 subjects with moderate to severe active RA inadequately controlled by TNFi therapy in the CL04041025 study. In the ongoing CL04041024 OLE study the long-term efficacy is shown preliminary by interim analysis results.

The completed clinical studies to date suggested that OKZ is effective in reducing disease symptoms in subjects with RA, compared with placebo, and that it is generally well tolerated (for further efficacy and safety information, refer to the most recent version of the IB). The safety profile of OKZ is consistent with the known effects of IL-6 blockers. Overall, the benefit/risk profile for subjects in this proposed study is favorable.

The design of this study contains adequate measures to mitigate risk factors and adequate safety monitoring to protect the subjects.

Taking the nonclinical and clinical data for OKZ into consideration, subjects should be monitored during clinical studies for potential AEs of infections and decreases in fibrinogen. In

addition, based on the mechanism of action of OKZ, subjects should be observed for events of dyslipidemia, increased liver transaminases and bilirubin, and decreases in neutrophils, which may be possible class effects (see Section 7.4.6.3 of the IB).

2.3.1 Expected Adverse Events and Reference Safety Information

From the safety data available to date, the following AEs are considered expected:

- Liver function test abnormalities (Medical Dictionary for Regulatory Activities [MedDRA] Preferred Terms [PTs] included alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, and liver function tests [LFT] abnormal);
- Elevations in total cholesterol, low-density lipoproteins (LDL), and triglycerides (MedDRA PTs included blood cholesterol increased, blood triglycerides increased, and hypertriglyceridemia);
- Reductions in neutrophil count (MedDRA PTs included neutropenia, neutrophil count decreased, leukopenia, and white blood cell count decreased);
- Increased incidence of infection (MedDRA PTs included influenza, nasopharyngitis, upper respiratory tract infections, and urinary tract infection); and
- Injection site reactions (MedDRA PTs included injection site erythema, injection site hematoma, injection site pruritus, and injection site reaction).

2.3.2 Anticipated Adverse Effects

Drug-class-related and disease-related events will be reported according to the Final Rule for Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (21 CFR Parts 312 and 320, 2011).

Drug Class-related Effects

Subjects treated with an IL-6 inhibitor should be aware that they may be at increased risk of experiencing the following events, which are PTs (unless otherwise specified) listed by System Organ Class (SOC):

1. Gastrointestinal disorders
   a) Diverticular perforation
2. Hepatobiliary disorders
   a) Any liver enzyme increase (medical judgment, not per MedDRA)
3. Immune system disorders
   a) Anaphylactic reaction
   b) Hypersensitivity
   c) Drug hypersensitivity
4. Infections and infestations
   a) Any infection (including serious infection) is anticipated, including, but not limited to:

   i) Pneumonia, cellulitis, herpes zoster, urinary tract infection, sepsis, gastroenteritis, upper respiratory tract infections, tuberculosis;
   ii) Opportunistic infections (eg, candidiasis, listeriosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, pneumocystis, nontuberculous mycobacteria, blastomycosis, or aspergillosis); and
   iii) Necrotizing fasciitis.
5. Investigations
   a) Neutrophil count decreased
   b) Platelet count decreased
   c) Any PT suggesting an elevation of blood lipid (medical judgment, not per MedDRA)
6. Vascular disorders
   a) Vascular hypertensive disorders (high-level term) not elsewhere classified (NEC)

The administration of products that contain protein may be associated with immunologic/allergic or nonimmunologic drug hypersensitivity reactions that could be severe. These reactions can occur as acute infusion, allergic, or delayed-type hypersensitivity reactions. Therefore, Investigators should only administer OKZ where medication and equipment for management of anaphylactic or anaphylactoid reactions are available. While injection site reactions have occurred, there have been no serious or severe systemic hypersensitivity reactions observed in the completed clinical studies to date.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of OKZ may be found in the IB. Details on the rationale for the study design, including dose selection, study-specific restriction such as food restrictions and selection of the study population is discussed in Section 4.2.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) will meet the requirements of European Union – Good Manufacturing Practice (EU GMP), ICH E6 GCP, Consolidated Guideline, current revision and all applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations, as well as Order No. 200n dated April 01, 2016 of the Ministry of Health of the Russian Federation on Approval of Rules for GCP.

3.0 OBJECTIVES AND ENDPOINTS

Table 6 Study Objectives and Endpoints

Objectives	Criteria for Evaluation (Endpoints)
Primary	
• To assess the effect of olokizumab (OKZ) on the pharmacokinetics (PK) of the Cytochrome P450 (CYP450) probe substrates, caffeine (CYP1A2), S-warfarin (CYP2C9), omeprazole (CYP2C19), and midazolam (CYP3A4) in subjects with rheumatoid arthritis	Primary • Area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{(0\text{-}inf)}$) for caffeine, omeprazole, and midazolam • AUC from time zero to the time "t" of the last quantifiable concentration ($AUC_{(0\text{-}last)}$) for S-warfarin • Maximum plasma concentration (C_{max}) for all cocktail substrates Secondary • Plasma $AUC_{(0\text{-}last)}$ or $AUC_{(0\text{-}inf)}$ (if not primary), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), elimination rate constant (λ_z), apparent systemic clearance (CL/F), and apparent volume of distribution (V_z/F) for cocktail parent compounds (caffeine, S-warfarin, omeprazole, and midazolam) • Plasma concentrations for OKZ
Secondary: Safety	
• To assess the safety and tolerability of the cocktail substrates when dosed in the presence or absence of OKZ • To assess the safety and tolerability of a single dose of OKZ in subjects with rheumatoid arthritis	• Assessment of adverse events (AEs), graded by Common Terminology Criteria for Adverse Events (CTCAE), physical examination, vital signs (blood pressure, pulse rate, and body temperature), standard 12-lead electrocardiogram (ECG), evaluation of laboratory parameters (clinical chemistry, hematology, and coagulation), and immunogenicity
Secondary: Pharmacodynamic	
• To assess the effect of OKZ on inflammatory markers (pharmacodynamics [PD]) in subjects with rheumatoid arthritis	• Interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations collected periodically throughout the study

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 1, open-label, 3-period, single-sequence, crossover study in subjects with RA with increased C-reactive protein (CRP) (≥1.2 × upper limit of normal [ULN]). During the study, subjects will be administered a cocktail of 4 substrates alone (Period 1) and in the presence of OKZ (Period 3). A single dose of 128 mg OKZ will be administered (Period 2) approximately 2 weeks prior to the second administration of the cocktail in Period 3. The cocktail comprises 100 mg caffeine (substrate of CYP1A2), 10 mg warfarin (containing 5 mg S-warfarin [substrate of CYP2C9]) plus 10 mg vitamin K, 20 mg omeprazole (substrate of CYP2C19), and 2 mg midazolam (substrate of CYP3A4) and will be administered after an overnight fast of at least 10 hours (Turpault et al, 2009). Serial blood samples will be collected to determine the PK of the cocktail substrate analytes and OKZ. Blood sampling for the measurement of IL-6 and CRP will also be performed.

Subjects will be screened within 35 days of the first dose administration and eligible subjects will be admitted to the study center on Day -1. The study will employ a 2-stage screening process; during the first Screening stage, assessments for genotyping, medical history with physical examination and FSH testing will be performed, as well as possibly the hepatitis serology and CRP screening assessments, if required by the study center. This will be followed approximately 3 weeks later by the second Screening stage, where the rest of the assessments will be conducted.

If a subject has a history of confirmed coronavirus disease 2019 (COVID-19) in the previous 3 months before Day 1 (or with sever or critical illness ever) or known exposure to an individual with confirmed COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within the past 2 weeks and it is revealed at the Screening Visit or prior to cocktail administration on Day 1, the subject should not be administered the study treatment, and further testing for COVID-19 is not required. In case a patient shows respiratory symptoms or informs the Investigator about contact with a COVID-19 infected person after drug administration the test for COVID-19 should be performed as soon as possible. Out of study positive RT-PCR results will be acceptable as well as following negative results, it is not necessary to repeat RT-PCR test in the site if the subject is considered recovered from COVID-19 by the local guidelines. If the Investigator suspects that a subject has contracted COVID-19, the Investigator should request feedback from the medical monitor and discuss this with the Sponsor.

Subjects whom tests positive for COVID-19 during the treatment period but before OKZ is administered (Day 8) will not be administered with OKZ and will be discontinued from the study. These subjects will however attend the End of Treatment (EOT) Visit after their recovery and the Safety Follow-up Visit. Subjects whom are dosed with OKZ (Day 8) and then tests positive for COVID-19 should attend the EOT Visit (Day 29) as well as the Safety Follow-up

Visit based on local guidelines for COVID-19 on Day 99 - with exception of the cases when it is not possible such as the cases with COVID-19 infection when the subject will come to the visit after recovery (subject should not be infectious at the time of EOT and follow-up visits) - and afterwards telephonic follow-up visits until 5 × OKZ $t_{1/2}$.

It is estimated that 15 subjects who meet the study eligibility criteria will need to be dosed in order to achieve the required 12 evaluable subjects. However, if necessary, additional subjects may be dosed to obtain the 12 evaluable subjects required.

On the morning of Day 1 after an overnight fast of at least 10 hours, subjects will receive the first treatment of the cocktail: 100 mg caffeine, 20 mg omeprazole, 10 mg warfarin, 2 mg midazolam (via syringe) followed by 10 mg vitamin K (via syringe [Zhuang et al, 2015]), orally, under the supervision of appropriately trained study center staff. The cocktail will be administered with 240 mL of water and all 4 cocktail substrates as well as the vitamin K should be ingested within 5 minutes (for details regarding study treatment administration, see Section 6.1).

Subjects will remain in the study center until Day 2 and will be discharged at the Investigator's discretion (ie, providing there are no safety concerns) after the 30-hour PK sample. Subjects will return to the study center on Day 3, Day 4, Day 6, and Day 8 for PK sampling (see Table 4 for PK sampling times).

On completion of the 7-day PK sampling period for the cocktail substrates on the morning of Day 8, subjects will be administered a single subcutaneous (SC) dose of 128 mg OKZ. All subjects will remain at the study center for at least 2 hours after the injection to be assessed for any systemic hypersensitivity reactions. Blood samples for determination of OKZ concentrations will be collected on Day 8 (predose [30-minute window allowed], along with the final PK sample collection for warfarin), Day 9, and Day 15. Subjects will attend the study center on an outpatient basis on Day 8, Day 9, and Day 15.

Subjects will be admitted to the study center on Day 21 and will receive the second administration of the cocktail substrates after an overnight fast of at least 10 hours on Day 22 (ie, 14 days after administration of OKZ, by which time maximum suppression of CRP is expected). Subjects will remain in the study center until the 30-hour PK samples (caffeine) have been taken on Day 23 and will return to the study center on Day 24, Day 25, Day 27, and Day 29 (EOT) for scheduled PK sampling (warfarin) (see Table 4 for PK sampling times). Blood sampling for determination of OKZ concentrations will be collected on Day 22 (prior to cocktail administration) and on Day 24 and Day 29 (see Table 5 for PK sampling times).

The IL-6 and CRP levels will be measured at Screening, prior to dose administration with the cocktail substrates on Day 1, prior to administration with OKZ on Day 8, and post OKZ administration on Day 9, Day 15, Day 22 (prior to dose administration of the cocktail), and Day 29, which will be considered the EOT Visit. Safety assessments will be performed at the EOT Visit (Day 29).

Subjects will be undergoing COVID-19 reverse transcription polymerase chain reaction (RT-PCR) testing. Two RT-PCR tests will be conducted, the second RT-PCR test will only be performed if the first test results are negative. Only subjects with a negative COVID-19 RT-PCR test result may be included in the study. Two consecutive RT-PCR tests will occur at Day -35 (Stage 1) - only if the Investigator suspects possible COVID-19 infection, at Day -3, Day 5, Day 19 and Day 29 (EOT) - obligatory. If the Investigator suspects possible COVID-19 infection, the RT-PCR tests should also be performed on Day 43. Only subjects with a negative COVID-19 RT-PCR test result may be administered the study drug on Day 8. The RT-PCR testing will be performed at local laboratories.

A rapid test will be conducted for the COVID-19 immunoglobulin G (IgG)/immunoglobulin M (IgM) testing at Screening–Stage 1 - only if the Investigator suspects possible COVID-19 infection, and prior to first inhouse period (Day -2) - obligatory. If the Investigator suspects possible COVID-19 infection, the IgG/IgM testing should also be performed prior to dose administration on Day 8 or/and prior to second inhouse period (Day 19) or/and Day 43. The serology will be performed onsite.

The Investigator's decision on COVID-19 infection should be based on patient's contacts, travels, presence or absence of any complaints, signs and symptoms suspicions for COVID-19 infection, local circumstance, or any other conditions if applicable.

The Safety Follow-up Visit on Day 99 ±7 days is scheduled at approximately 3 × OKZ terminal half-life ($t_{1/2}$). Subjects who discontinue the study early, should be asked to return for an EOT and Safety Follow-up Visit - with exception of the cases when it is not possible such as the cases with COVID-19 infection when the subject will come to the visit after recovery (subject should not be infectious at the time of EOT and follow-up visits). There will be 2 additional telephone follow-up calls, with the subject, on Day 130 ±7 days and Day 161 ±10 days after the EOT, at approximately 4 × OKZ $t_{1/2}$ and 5 × OKZ $t_{1/2}$, respectively.

4.2 Scientific Rationale for Study Design

Olokizumab has been shown to reverse the inhibitory effect of IL-6 on the activity of CYP450 isozymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5, and on the activity of NTCP in vitro (Study NCD2107).

To support the registration of OKZ, R-Pharm proposes a single-cocktail drug-drug interaction study design in subjects with RA to evaluate any potential effects of OKZ on the metabolism of substrates selective for specific CYP450 activity. The following probe substrates will be studied in the planned cocktail study: caffeine (CYP1A2), S-warfarin (CYP2C9), omeprazole (CYP2C19), and midazolam (CYP3A4). The planned substrates are specific for the indicated CYP450 isozymes, and a previous study has shown that there were no interactions between the individual substrates when administered in combination as cocktail (Turpault et al, 2009).

Currently, there are no plans to study CYP2B6 or NTCP. Study NCD2107 showed in vitro that the effect of OKZ on recombinant human IL-6-mediated suppression of CYP2B6 activity was similar to that of CYP2C19 and CYP3A4 activity, and less effect compared with CYP2C9 activity. Therefore, results from the planned cocktail study for CYP1A2, CYP2C19, CYP2C9, and CYP3A4 are expected to be representative for the spectrum of potential reversal of the inhibitory effect of IL-6 on CYP450 activity.

The fasting restrictions are based on those typically used for healthy volunteer studies and are in general based on the FDA Guidance for Bioavailability and Bioequivalence Studies (FDA Guidance for Bioavailability and Bioequivalence Studies).

The proposed study will be conducted in subjects with RA as it is not possible to assess the reversal of IL-6-induced suppression in healthy subjects with normal IL-6 levels. As there is an inverse correlation between IL-6 or CRP levels and CYP450-metabolized drug clearance (Rivory et al, 2002; Frye et al, 2002; Machavaram et al, 2013), a threshold CRP (ie, ≥1.2 × ULN) will be utilized as an inclusion criterion. This will ensure that the selected RA population is sufficiently sensitive to any potential cytokine-modulating activity of OKZ.

A single dose of 128 mg OKZ has been selected. This design limits the exposure of subjects with RA to a single dose treatment, where there is no prospect of direct therapeutic benefit.

Given similar human and cynomolgus monkey physiology during pregnancy, and the observed increased risk of dystocia and hemorrhage at delivery, inhibition of IL-6 signaling during pregnancy is not recommended. Therefore, female subjects of childbearing are eligible to participate in this study only if they continue to have negative pregnancy test and agree to use a highly effective contraception methods (see Appendix 6) during the study starting from the screening (signed ICF) and for 6 months after OKZ dosing (irrespectively if the subject continues the study till end of study (EOS) visit per protocol or not).

Justification for Dose

It has been previously demonstrated that a single dose of a cytokine modulator can reverse IL-6 mediated suppression of CYP450 activity (Schmitt et al, 2011; Zhuang et al, 2015; Zhou & Meibohm, 2013). Administration of a SC dose of OKZ at 1 mg/kg was associated with maximum CRP suppression (Study RA0010) obtained at 14 days postdose. At this dose, a maximum reduction in IL-6 was observed on Day 28 (first postdose IL-6 sample collection in Study RA0010), and suppression was maintained through the final IL-6 sample collection on Day 84. Olokizumab C_{max} following a dose of 1 mg/kg SC ranged from 3.19 to 12.5 µg/mL (geometric mean: 6.29 µg/mL) and occurred at a median time to C_{max} (t_{max}) of 313 hours (range: 48.0 to 648 hours). Olokizumab concentrations will be measured periodically throughout the study.

Due to an increase in the concentration of the formulation, it should be noted that the volume used in this Phase 1 study (0.8 mL) results in a dose of 128 mg rather than 120 mg. This change will allow the objectives of the study to be met and it was not expected that there should be an impact on safety of the subjects.

The planned single dose of 128 mg OKZ exceeds the OKZ dose which previously elicited full CRP and IL-6 suppression. Olokizumab was well tolerated at repeat SC doses of up to 240 mg q2w over a maximum dosing period of 12 weeks, or 120 mg q2w over a maximum dosing period of 48 weeks. Olokizumab doses in the Phase 3 program were 64 mg q4w and 64 mg q2w (ie, 64 and 128 mg/month). Based on an approximate half-life of 31 days, an approximately 2.1-fold to 3.7-fold OKZ accumulation is anticipated for the q4w and q2w regimens, respectively; hence exposure following a single dose of 128 mg approximates that of the lower 64 mg q4w dose. Because maximum IL-6 suppression is anticipated at the 128 mg OKZ dose, it is considered sufficiently high to adequately characterize potential cytokine modulating activity by OKZ.

Assessment of the potential reversal of IL-6-mediated down-regulation of CYP450 activity by OKZ will be evaluated once, 14 days after OKZ administration. This schedule coincides with full CRP suppression (Study RA0010). The scheduled cocktail coadministration is close to the median t_{max} observed following 1 mg/kg SC OKZ but is later than the median t_{max} observed following 3 g/kg SC OKZ (171 hours [range: 144 to 478 hours]). Cocktail administration 14 days after the OKZ dose has been selected to ensure that the maximum effect of OKZ on CYP450 activity is evaluated, based on CRP and IL-6 suppression, and to allow time for CYP450 upregulation, especially for CYP3A4. R-Pharm considers a single timepoint comparison to be sufficient. It is anticipated that OKZ reversal of CYP450 activity suppression will be maintained for at least 3 to 4 × the half-life of OKZ. Any evaluation of the duration of the effect of OKZ on CYP450 activity would pose an undue burden on the subjects dosed in this study.

4.3 End of Study Definition (Clinical Part)

The end of the study is defined as the date of the last scheduled procedure, ie, telephonic follow-up on Day 161 ±10 days, shown in the Schedule of Activities (SoA) (see Table 3) for the last subject in the study globally.

4.4 Dose Escalation Criteria

Not applicable.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

Approximately 15 eligible subjects will be enrolled at approximately 3 study centers to have at least 12 evaluable subjects completing the study. However, if necessary, additional subjects may be dosed to obtain the 12 evaluable subjects required. Participating subjects should have a diagnosis of RA and be on a stable dose of MTX (see inclusion criterion #5).

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subjects willing and able to give voluntary informed consent and sign an Informed Consent Form (ICF).
2. Male or female subjects aged ≥18 to ≤70 years of age.
3. Male subjects and their female partners and female subjects of childbearing potential* must agree to adhere to the contraceptive requirements for the study (see Appendix 6).

   *Female subjects of nonchildbearing potential must be:

   a. Surgically sterile (ie, documented bilateral tubal ligation or removal of both ovaries and/or uterus at least 6 months prior to first dosing), or

   b. Naturally postmenopausal (spontaneous cessation of menses) for at least 24 consecutive months prior to first dosing, with a follicle-stimulating hormone level at Screening of ≥40 mIU/mL.

4. Body mass index of 18 kg/m^2 to 29.9 kg/m^2, inclusive, and body weight of 55 kg to 110 kg, inclusive, if male, and 45 kg to 100 kg, inclusive, if female.
5. Subjects must have a diagnosis of adult onset RA classified by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 revised classification criteria for RA (Aletaha et al, 2010) for at least 12 weeks prior to Screening. If the subject was previously diagnosed according to ACR 1987 criteria, the Investigator may classify the subject per ACR 2010 retrospectively, based on medical history, and using available source data.
6. Subjects must have received MTX, sulfasalazine, or hydroxychloroquine for at least 12 weeks prior to Day 1 and in stable dose for at least 6 weeks prior to Day 1 without significant AEs. Stable doses of MTX should be 10 mg to 25 mg weekly with folic acid (at least 5 mg weekly or equivalent). No significant side effects based on the

Investigator's judgment should be observed during treatment by these agents. The maximum allowed doses of sulfasalazine and hydroxychloroquine are:

a. Sulfasalazine: 3 g per day
b. Hydroxychloroquine: 400 mg per day

Note: The doses should remain stable and not be changed from the time of signing the ICF until the end of the treatment period (EOT, Day 29).

7. Subjects must have an increased CRP at Screening (of ≥1.2 × ULN).

8. Female subjects of childbearing potential must have negative pregnancy test at Screening and throughout the study until the end of study (EOS, Day 161).

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Diagnosis of any other inflammatory arthritis or systemic inflammatory disease (eg, gout, psoriatic or reactive arthritis, Crohn's disease, Lyme disease, juvenile idiopathic arthritis, or systemic lupus erythematosus). Osteoarthritis is classified as a degenerative disease rather than an inflammatory disease.

2. Subjects with Steinbrocker Class III or IV functional capacity (incapacitated, largely, or wholly bed ridden, or confined to a wheelchair, with little, or no self-care).

3. Prior exposure to any licensed or investigational compound directly or indirectly targeting IL-6 or IL-6R within 12 months of Day 1.

4. Treatment with DMARDs other than MTX, hydroxychloroquine, or sulfasalazine. Treatment with the following DMARDs are not allowed within the specified time period prior to Day 1:

    a. 4 weeks for azathioprine, cyclosporine, chloroquine, gold, penicillamine, minocycline, or doxycycline.

    b. 12 weeks for leflunomide unless the subject has completed the following elimination procedure at least 4 weeks prior to Day 1: Cholestyramine at a dosage of 8 grams 3 times daily for at least 24 hours or activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours.

    c. 24 weeks for cyclophosphamide.

5. Treatment with any cell-depleting therapies including anticluster of differentiation (CD)20 or investigational agents (eg, CAMPATH®, anti-CD4, anti-CD5, anti-CD3, and

anti-CD19) with the exception of rituximab. Treatment with rituximab is not allowed within 6 months of Day 1.

6. Treatment with TNFi (including investigational proposed or licensed biosimilars) or any other biologic therapy for the treatment of RA within 12 weeks of Day 1.
7. Use of parenteral or intra-articular glucocorticoids within 4 weeks prior to Day 1.
8. Use of oral glucocorticoids greater than 10 mg/day prednisone (or equivalent) or change in dosage within 4 weeks prior to Day 1.
9. Use of indomethacin and ketorolac; other nonsteroidal anti-inflammatory drugs (NSAIDs) (with the exception of aspirin, see below) must be taken at a stable dose and route of administration for at least 2 weeks prior to Day 1.
10. Female subjects of nonchildbearing potential taking hormone replacement therapy within 4 weeks prior to Day 1.
11. Vaccination with live vaccines in the 6 weeks prior to Day 1 or planned vaccination with live vaccines during the study.
12. Participation in any other investigational drug study within 30 days or 5 times the $t_{1/2}$ of the investigational drug, whichever is longer, prior to Day 1.
13. Use of aspirin or other antiplatelet agents and anticoagulants including warfarin in the 4 weeks prior to Day 1.
14. Has received any prescription or nonprescription drugs or other products (eg, herbal preparations, food products) known to be inhibitors/inducers of CYP3A4, CYP2C9, CYP2C19, or CYP1A2 within 4 weeks prior to Day 1 and for the duration of the study up to the EOT (Day 29) Visit. See Appendix 4 for a list of inhibitors and inducers. The use of MTX, as described in inclusion criterion #5, is permitted.
15. Use of any herbal preparations (including foods or beverages containing herbal preparations), dietary supplements, or natural medications within 14 days of Day 1.
16. Has received midazolam and/or omeprazole (or esomeprazole) within 14 days of Day 1.
17. Excessive intake of caffeine (more than 5 cups of coffee or equivalent per day) and the inability to abstain from caffeine-containing drinks and foods from 2 days prior to each cocktail administration and while inpatient (Day -1 to Day 2 and Day 21 to Day 23, respectively).
18. Poor metabolizers of CYP2C9 (genotype *2/*2, *2/*3, *3/*3) or CYP2C19 (genotype *2/*2, *2/*3, *3/*3), ultra-rapid metabolizers of CYP2C19 (*17/*17), or high sensitivity to warfarin (VKORCI genotype AA).

19. Previous participation (enrolled) in this study or another study of OKZ in case of receiving at least one OKZ dose.

20. Abnormal laboratory values as defined below. If, in the opinion of the Investigator, exclusionary results are due to laboratory error or a transient condition, these tests may be repeated once during Screening.

    a. Creatinine level ≥1.5 mg/dL (132 µmol/L) for females or ≥2.0 mg/dL (177 µmol/L) for males.

    b. ALT or AST level ≥1.5 × ULN.

    c. Platelets $<150 \times 10^9$/L ($<150{,}000/mm^3$).

    d. White blood cell count $<3.0 \times 10^9$/L.

    e. Neutrophil count $<2.0 \times 10^9$/L ($<2{,}000\ mm^3$).

    f. Hemoglobin level ≤95 g/L.

    g. Glycosylated hemoglobin (HbA1c) level ≥8%.

    h. International normalized ratio above the ULN (Normal range: 0.80 or 0.90 to 1.20, males and females of all ages).

21. Subjects with concurrent viral hepatitis B or C infection as detected by blood tests at Screening (eg, positive for hepatitis B surface antigen [HBsAg], hepatitis B DNA [HBV DNA] or hepatitis C virus antibody [HCV Ab]).

    a. HBV DNA to be tested only in anti-hepatitis B core antigen [anti-HBc] positive subjects.

    b. Subject who is positive for hepatitis B surface antibody (anti-HBs) and total anti-HBc but negative for HBsAg and HBV DNA, will be eligible upon qualified specialist (i.e. hepatologist) consultation with documented conclusion no additional risk is suspected for the subject.

    c. Subject who is positive for hepatitis B surface antibody (anti-HBs) but negative for HBsAg and total anti-HBc, will be eligible with no additional consultation.

22. Subjects with human immunodeficiency virus (HIV) infection.

23. Subjects with:

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

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

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

d. Positive IGRA result at Screening. If indeterminate, the IGRA can be repeated once during Screening. If there is a second indeterminate result, the subject will be excluded.

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

25. Subjects with a history of major bleeding, bleeding tendencies (such as any prior gastrointestinal bleeding and recent ulceration of gastrointestinal track, congenital and acquired disorders by hemostasis), or other clinically significant predisposition to bleeding according to the physician's judgment.

26. Subjects with a history or presence of severe cardiovascular conditions such as stroke, transient ischemic attack, or myocardial infarction in medical history.

27. Uncompensated congestive heart failure, or Class III, or IV heart failure defined by the New York Heart Association classification (see Appendix 5).

28. Untreated, uncontrolled, or resistant arterial hypertension Grade 2 to 3 (systolic blood pressure [BP] >160 mm Hg and/or diastolic BP >100 mm Hg, based on the mean of 3 readings). If hypertension is not controlled, subjects should be excluded, and not allowed for rescreening.

29. Uncontrolled diabetes mellitus (based on the Investigator’s judgment).

30. Subjects with a history or presence of any other cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, dermatological, neurological, psychiatric, hematological, or immunologic/immunodeficiency disorder(s) or any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator’s judgment, contraindicate subject participation in the clinical study, or clinically significant enough in the opinion of the Investigator to alter the disposition of the study treatment, or constitute a possible confounding factor for assessment of safety of the study treatment.

31. Subjects with gastrointestinal (GI) resection (eg, partial or total gastrectomy) likely to interfere with absorption of study treatment.

32. Subjects with any infection requiring any anti-infective therapy (eg, antibiotic, antiviral, or antifungal therapy) in the 4 weeks prior to Day 1, or serious or recurrent infection with history of hospitalization in the 6 months prior to Day 1 or active infection on Day 1.

33. Subjects with evidence of disseminated herpes zoster infection, zoster encephalitis, meningitis, or other nonself-limited herpes zoster infections in the 6 months prior to Day 1.

34. Subjects with planned surgery during the study (up to and including the EOT Visit, [Day 29]) or surgery ≤4 weeks prior to Screening and from which the subject has not fully recovered, as judged by the Investigator.

35. Subjects with diverticulitis or other symptomatic GI conditions that might predispose the subject to perforations, including subjects with a history of such predisposing conditions (eg, diverticulitis, GI perforation, or ulcerative colitis).

36. History of chronic alcohol or drug abuse or consumption of more than 21 units (male subjects) or 14 units (female subjects) of alcohol a week (unit = 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer) as judged by the Investigator.

37. Current smokers or those who have smoked or used nicotine products within the previous 3 months prior to Screening.

38. Subjects with a known hypersensitivity or contraindication to any component of the cocktail drugs or OKZ.

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

40. Any self-reported symptoms of influenza-like or COVID-19 like illness in the 14 days preceding Screening OR Day 1 as per the Investigators assessment. Symptoms related to COVID-19 include, but are not limited to:

    a. Respiratory symptoms (eg, sore throat, nasal congestion, post-nasal discharge, wheezing, cough, dyspnea, and bronchial breath sounds);

    b. Non-respiratory symptoms, such as gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea), neurologic symptoms (eg, anosmia, ageusia, headache), myalgia or fatigue.

41. Active SARS-CoV-2 infection as confirmed by RT-PCR or/and positive serology at Screening.

42. Known exposure to an individual with confirmed COVID-19 or SARS-CoV-2 infection within 2 weeks before Screening OR Day 1.

43. History of COVID-19 infection in the previous 3 months before Day 1 or with sever or critical illness ever.

    Note: The subject can be enrolled if all of the following criteria are fulfill:

    1) had non-sever or non-critical COVID-19 infection more than 3 months before Day 1;

    2) fully recovered as per official medical records which should be documented as a source document (mild sequalae of the previous infection such as dry cough, weakness should be resolved by the time of Screening);

    3) there are no any concerns that the subject is infections to others;

    4) there are no any other local guidelines/requirements with regards of this group of subjects.

44. Those subjects who have been at high risk of exposure before Screening, including but not limited to: Close contacts of confirmed COVID-19 cases, anyone who had to self-isolate as a result of a symptomatic household member, frontline healthcare professionals working in accident and emergency (A&E), ICU and other higher risk areas.

45. Individuals currently working with high risk of exposure to SARS-CoV-2 (eg, active healthcare workers or emergency response personnel having direct interactions with or providing direct care to patients).

46. Pregnancy and breastfeeding.

47. Other medical or psychiatric conditions or laboratory abnormalities that may increase potential risk associated with study participation and administration of study treatment, or that may affect study results interpretation and, as per the Investigator's judgment.

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

49. Employees or relatives of the Sponsor, Contract Research Organization, or the study center personnel.

5.3 Lifestyle Considerations

5.3.1 Concomitant Medications

1. Subjects must avoid concomitant medications, herbal preparations, and/or ingestion of foods with known inducer/inhibitory effects on CYP1A2, CYP2C19, CYP2C9, and CYP3A4 through Day 29 (See Appendix 4 for a list of these).

2. Subjects must not take medication that could adversely affect GI motility or transit (eg, diphenoxylate, loperamide, metoclopramide, cisapride, tegaserod, erythromycin) from 7 days prior to each administration of the cocktail drugs (Day 1 and Day 22) through the 48 hours following each cocktail administration.

5.3.2 Dietary, Caffeine, Alcohol and Tobacco Restrictions

1. Subjects are to abstain from taking caffeine-containing drinks or foods (eg, coffee, tea, cocoa, chocolate, and cola) from 48 hours prior to each cocktail administration and while inpatient (Day -1 to Day 2 and Day 21 to Day 23, respectively). During the outpatient period Days 2 to 20 subjects are to avoid high caffeine-containing energy drinks (eg, Red Bull) and will be provided with decaffeinated tea and coffee by the study center.
2. Subjects are to refrain from intake of alcohol within the 48 hours prior to Day 1 until the final warfarin PK sample on Day 8 and within 48 hours of Day 22 until the final warfarin PK sample on Day 29 (EOT). During the outpatient period Day 8 to Day 20, alcohol consumption should be limited to no more than 2 units per day.
3. Subjects are to maintain their normal diet throughout the study and not implement any changes.
4. The cocktail will be administered with 240 mL water after an overnight fast of at least 10 hours. See Table 9 for detailed requirements regarding fasting at study assessment visits.
5. Subjects are to attempt to avoid passive (secondhand) smoking from 2 weeks prior to the first dose of cocktail administration until after the last PK sample is collected on Day 29 (EOT) of the study.
6. Subjects are not to consume any grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges from at least 1 week prior to the first dose of cocktail administration (Day 1) until after the last PK sample (EOT, Day 29).

5.3.3 Contraception

Male subjects and their female partners and female subjects of childbearing potential are to adhere to the contraceptive requirements for the study. See Appendix 6 for details regarding contraceptive requirements.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the reason for the screen failure no longer exists (with exception of the subjects with arterial hypertension in case hypertension is not controlled). Rescreened subjects should not be assigned the same subject number as for the initial screening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), and marketed product(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatment(s) Administered

The details of the study treatment(s) administered are presented in Table 7.

Table 7 Study Treatment Details

	Study Treatment	**Cocktail**			
Study Treatment Name:	Olokizumab	Caffeine	Warfarin	Omeprazole	Midazolam
Dosage Formulation:	Sterile solution for subcutaneous (SC) injection	Tablet	Warfarin Tablet plus vitamin K-solution for intravenous injection to be taken orally	Tablet	Syrup to be taken orally
Unit Dose Strength(s)/Dosage Level(s):	128 mg (0.8 mL injection)	100 mg	10 mg 10 mg/mL	20 mg	2 mg/mL
Route of Administration:	SC injection	Oral	Oral	Oral	Oral
Dosing Instructions:	Subjects will receive a single dose of OKZ 128 mg via SC injection (0.8 mL) by study center staff on Day 8	Subjects will receive an oral administration of a cocktail of substrates (100 mg caffeine, 20 mg omeprazole, 10 mg warfarin, 2 mg midazolam [via syringe] followed by 10 mg vitamin K [via syringe], on 2 occasions, on the morning of Day 1 and Day 22 (±1). The cocktail will be administered with 240 mL water after a 10 hour overnight fast. The interval in which all 4 cocktail substrates and vitamin K are administered and ingested should be within 5 minutes. Subjects will continue to fast until 4 hours postdose. All doses will be administered under the supervision of a suitably qualified study center staff member. Immediately after tablet administration, visual inspection of the oral cavity will be performed for each subject. The midazolam solution will be administered directly into the subject's mouth by syringe by a study center staff member and then immediately washed down with water. The vitamin K solution will be administered directly into the subject's mouth by syringe and then immediately washed down with water (Zhuang et al, 2015) In total each subject will drink 240 mL water with the cocktail medications.			
Packaging and Labeling:	Study treatment will be provided in commercially available secondary packages for the cocktail and in cartons for OKZ. Each package or carton will be labeled as per country requirements. Each subject will receive their own package and sharing is not permitted.				

Manufacturer:	R-Pharm International	Purchased by a 3rd party and distributed to study centers from a central depot

For the cocktail administration, the timings of food and fluid intake up to 24 hours postdose are detailed in Table 8:

Table 8 Timing of Fluid and Food Intake Around Cocktail Administration

Time	Food and fluid details
Evening of previous day	Evening meal
From 22:00 on previous day	Fast from food and fluids except water
From 1-hour predose (9 hours after the last meal)	No fluids allowed including water
At dosing (10 hours after the last meal)	240 mL water administered with the cocktail medications
From 2 hours postdose	Free access to water
Approximately 4.5 hours postdose	Lunch
Approximately 7.5 hours postdose	Afternoon snack
Approximately 11 hours postdose	Evening meal
After 24 hours postdose assessments	Breakfast

Reference = FDA Guidance for Bioavailability and Bioequivalence Studies (FDA Guidance for Bioavailability and Bioequivalence Studies)

The study pharmacist or designee will prepare the OKZ syringes for SC injection. The solution may remain in the syringe for a maximum of 4 hours prior to its injection. The SC syringes should be warmed at room temperature prior to handing to the study center staff for SC injection. Qualified study center staff will administer a single SC injection (0.8 mL of OKZ) on Day 8 in either the abdomen or the thigh. All subjects will remain at the study center for at least 2 hours following the administration of OKZ to be assessed for onset of any systemic injection reactions.

The date, time, and location of the SC injection should be recorded in the electronic Case Report Form (eCRF). The Investigator should also record in the eCRF whether or not the full dose was injected.

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

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

2. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label, nonrandomized study, therefore no randomization of subjects will occur. No blinding procedures are applicable.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. All dates and times of study treatment administration and any departures from the intended regimen must be recorded on the eCRFs.

All study treatment administrations will be performed in the study center under the supervision of appropriately trained staff. A mouth check will be performed following oral administration. A monitor will review the pharmacy records at each study center including the drug dispensing records or drug accountability forms. The pharmacist (or designee) should record all study treatment dispensed to subjects on the eCRFs.

6.5 Emergency Treatment Strategy

The study center staff is responsible for the ongoing safety and wellbeing of the subjects while they are in the study center. There is a paging system to alert the staff to any area in the center where a subject may need medical attention. In the case of an emergency, equipment and emergency drugs are available to treat common medical emergencies that might occur in a Phase 1 study. If necessary, the clinical staff can contact on-call physicians or public emergencies services in the event of a serious medical event.

6.6 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency; and
- Mode of administration.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of excluded medications/therapy is provided in Appendix 4.

Paracetamol/acetaminophen, at doses of ≤2 gram/day, is permitted for use any time during the study with the exception of within 24 hours prior to joint assessment. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor, if required.

6.7 Dose Modification

Dose modifications are not planned or allowed in this study.

6.8 Treatment after the End of the Study

The Sponsor will not provide any care to subjects after they leave the study because subjects will be on their standard RA maintenance care.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

If a subject who does not meet enrollment criteria is inadvertently enrolled, the Sponsor or Sponsor designee must be contacted, and that subject must be discontinued from study treatment after confirmation with the PK specialist and Sponsor.

Study treatment administration for any individual subject will be stopped if the subject experiences an SAE or a clinically significant possibly drug-related AE, which in the opinion of the Principal Investigator, or Sponsor's medical representative, warrants discontinuation of the study and/or study treatment for that subject's wellbeing.

Subject who discontinue the study treatment early, should be asked to return for an End of Treatment (EOT) (Day 29) and Safety Follow-up Visit (Day 99) - with exception of the cases when it is not possible such as the cases with COVID-19 infection when the subject will come to the visit after recovery (subject should not be infectious at the time of EOT and follow-up visits). After that an End of Study (EOS) visit should be performed. See the SoA (Table 3) for data to be collected at the time of EOT, Safety Follow-up and EOS Visit and for any further evaluations needed to be completed.

7.1.1 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 × ULN with total bilirubin ≤2 × ULN after repeat laboratory testing;
- Subjects have an active or clinically significant infection; or
- 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 (eg, 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 judgment or other clinically significant newly diagnosed comorbidity that requires additional assessments for

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

7.1.2 Permanent Discontinuation of Study Treatment

In addition to the above, study treatment will be discontinued permanently 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 the Sponsor or designee is to be notified.
- Subject presents with any of the following elevated liver function tests (LFTs):
  - ALT or AST elevations >8 × ULN at any time, regardless of total bilirubin or accompanying symptoms.
  - ALT or AST >5 × ULN for ≥2 weeks regardless of total bilirubin or accompanying symptoms. The elevation should be continuous for ≥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 study treatment should be discussed on a case-by-case basis.
  - ALT or AST elevations >3 × ULN and total bilirubin value >2 × ULN at any time.
  - AST or ALT elevations >3 × ULN accompanied by symptoms which, as determined by the Investigator, are the result of hepatic injury (eg, 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 $<500\times10^6$/L ($<500/mm^3$)
  - Two sequential lymphocyte counts $<500\times10^6$/L ($<500/mm^3$)
  - Platelet count $<50\times10^9$/L ($<50{,}000/mm^3$ or $<50{,}000 \times 10^6$/L)
  - Two sequential hemoglobin values ≤8.0 g/dL and decreased ≥20 g/L (2 g/dL) below baseline
  - Creatinine value >2 × ULN
- If the subject tests positive for COVID-19 or SARS-CoV-2 (RT-PCR testing or IgM testing).
- Subject has a GI perforation.
- Subject diagnosed with diverticulitis.
- Subject has a confirmed active TB.
- 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.
- Pregnancy of female subject.

7.2 Subject Discontinuation/Withdrawal from the Study

The criteria for enrollment are to be followed explicitly.

If a subject who does not meet enrollment criteria is inadvertently enrolled, the Sponsor or designee must be informed immediately, and the subject may be discontinued from the study.

If, in the opinion of the Investigator, a subject is consistently noncompliant with the protocol in regards to study procedures, use of concomitant medications, or dosing with the study treatment, the Sponsor or designee must be informed as soon as it can be possible, and the case will be reviewed by the Sponsor on a case-by-case basis and the noncompliant subject can be discontinued from the study.

A subject should be discontinued from the study in the following circumstances:

- Subject is unwilling to continue the study participation (informed consent withdrawal). If the subject discontinues from the study, the Investigator should inquire about the reason for discontinuing.
- Subject is lost to follow-up (see section 7.3).
- Death of subject.
- The Sponsor, Investigator, a regulatory agency, or an ethical committee stops the study for any reason (see Appendix 2).

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. Appropriate standard of care, at the discretion of the Investigator, will be initiated.

If the study is discontinued the End of Study (EOS) Visit should be completed.

Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Subjects withdrawing due to an AE should be followed up according to the section 8.2.10.

Subjects who voluntarily withdraw are termed dropouts. Dropouts and subjects withdrawn due to protocol violations will not be replaced.

Additional subjects may be dosed to obtain the 12 fully eligible subjects.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the study center for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Table 3).

Protocol waivers or exemptions are not allowed (See Section 5.0).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA (see Table 3) is essential, and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed the normal amount of blood (450 mL) collected during such studies. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Unscheduled Visits will be allowed at the Investigator's discretion if deemed necessary for the subject's safety and wellbeing. At this visit, any of the assessments from the SoA (see Table 3) may be performed dependent on the presenting reason. The Sponsor or Sponsor's designee should be informed of these incidents in a timely fashion.

A tabular representation of the study assessments per visit is presented in Table 9.

Table 9 Tabular Outline of Study Assessments

Study period	Study Window	Day	Assessments to be performed[a]
Screening Stage 1	Day -35 to Day -14		Informed consent, inclusion/exclusion, physical examination, genotyping, medical history, FSH, hepatitis serology[b], AEs/SAEs, CRP[c], and, only if the Investigator suspects possible COVID-19 infection - COVID-19 RT-PCR testing[e] and COVID-19 IgM/IgG testing (using rapid testing)
Screening Stage 2	Day -14[d] to Day -1		Inclusion/exclusion, demography, height and weight, physical examination, vital signs, ECG, blood pregnancy test for WOCBP, TB risk questionnaire, chest radiography, QuantiFERON-TB Gold Plus, HIV serology, hepatitis serology[b], drugs of abuse, HbA1c, hematology, chemistry panel, urinalysis, coagulation panel, AEs/SAEs, concomitant medication, IL-6, and CRP[c] samples
	Day -3 to Day -2		Physical examination, COVID-19 RT-PCR testing[e] and COVID-19 IgM/IgG testing (using rapid testing)
	Day -1	Day -1	Admission, medical history, inclusion/exclusion, physical examination, vital signs, ECG, urine pregnancy test for WOCBP, drugs of abuse, cotinine and alcohol screen, coagulation panel, AEs/SAEs, concomitant medication
Period 1	Day 1 to Day 6	Day 1	Predose: weight, DAS28 assessment, and IL-6/CRP samples, additional blood sampling for future genotype testing Cocktail PK samples (predose - see Table 4 for details)
			Administer cocktail after 10-hour overnight fast. See Table 8 for details Cocktail administration (see Table 7 for details) Cocktail PK samples (postdose - see Table 4 for details), AEs/SAEs, concomitant medication
		Day 2 to Day 6	Cocktail PK samples (see Table 4 for details), INR only[f], AEs/SAEs, concomitant medication, and COVID-19 RT-PCR testing[e] (Day 5 only). Results for the RT-PCR tests should be available before OKZ are administered on Day 8
Period 2	Day 8 to Day 21	Day 8	Predose: COVID-19 IgM/IgG testing (using rapid testing) - only if the Investigator suspects possible COVID-19 infection, collect final warfarin PK sample, DAS28 assessment, weight, physical examination, vital signs, ECG, urine pregnancy test for WOCBP, IL-6/CRP samples, hematology, chemistry panel, coagulation panel, drugs of abuse, cotinine and alcohol screen, AEs/SAEs, concomitant medication, assess injection site reactions, cocktail and OKZ PK samples (predose – see Table 4 and Table 5 for details), and ADAs[g]
			Administer OKZ, assess injection site reactions, cocktail and OKZ PK samples (postdose – see Table 4 and Table 5 for details), AEs/SAEs, concomitant medication

Study period	Study Window	Day	Assessments to be performed[a]
		Day 9	Assess injection site reactions, OKZ PK samples (see Table 5 for details), AEs/SAEs, concomitant medication, IL-6/CRP samples
		Day 15	OKZ PK samples (see Table 5 for details), AEs/SAEs, concomitant medication, IL-6/CRP samples
		Day 19	Physical examination, COVID-19 RT-PCR testing[e], and, only if the Investigator suspects possible COVID-19 infection - COVID-19 IgM/IgG testing (using rapid testing)
		Day 21	Admission, urine pregnancy test for WOCBP, drugs of abuse, cotinine and alcohol screen, INR only[f], AEs/SAEs, concomitant medication
Period 3	Day 22 to Day 29	Day 22	Predose: weight, physical examination, OKZ PK samples (see Table 5 for details), AEs/SAEs, concomitant medication, and IL-6/CRP samples Cocktail PK samples (see Table 4 for details for details)
			Administer cocktail after 10-hour overnight fast. See Table 8 for details Cocktail administration (see Table 7 for details), cocktail PK samples (see Table 4 for details)
		Day 23	Cocktail PK samples (see Table 4 for details), INR only[f], AEs/SAEs, and concomitant medication
		Day 24	Cocktail PK samples (see Table 4 for details), OKZ PK samples (see Table 5 for details), INR only[f], AEs/SAEs, concomitant medication
		Day 25	Cocktail PK samples (see Table 4 for details), INR only[f], AEs/SAEs, concomitant medication
		Day 27	Cocktail PK samples (see Table 4 for details), INR only[f], AEs/SAEs, concomitant medication
		Day 29	(EOT): DAS28 assessment, weight, physical examination, vital signs, ECG, urine pregnancy test for WOCBP, OKZ PK samples (see Table 5 for details), Cocktail PK samples (see Table 4 for details), hematology, chemistry panel, urinalysis, coagulation panel, AEs/SAEs, concomitant medication, IL-6 and CRP samples, ADAs[g], and COVID-19 RT-PCR testing[e]
Safety Follow-up	Day 30 to Day 161	Day 43	(Telephonic): Physical examination, COVID-19 RT-PCR testing[e] (only if the Investigator suspects possible COVID-19 infection), and, only if the Investigator suspects possible COVID-19 infection - COVID-19 IgM/IgG testing (using rapid testing)[h]
		Day 99	(SFU): Physical examination, vital signs, urine pregnancy test for WOCBP, hematology, chemistry panel, AEs/SAEs, concomitant medication, ADAs[g]
		Day 130	(Telephonic): AEs/SAEs, concomitant medication
		Day 161	(Telephonic, EOS): AEs/SAEs, concomitant medication

Abbreviations: ADA = antidrug antibody; AE = adverse event; COVID-19 = Coronavirus disease 2019; CRP = C-reactive protein; DAS28 = Disease Activity Score 28 joint count; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin A_{1c}; HIV = human immunodeficiency virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IL-6 = interleukin-6; INR = international normalized ratio; OKZ = olokizumab; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SFU = safety follow-up; TB = tuberculosis; WOCBP = woman of childbearing potential.

[a] Food restriction: none, except as indicated in inclusion/exclusion and restrictions, with the exception of an overnight fast ahead of cocktail administration.

[b] Hepatitis serology and CRP screening assessments could be performed during Screening Stage 1, if required by the study center.

[c] The CRP test to assess eligibility can be done during the first stage of Screening and can be repeated once during Screening, provided results arrive prior to the admission date. No extensions of the Screening period will be granted for missing laboratory data unless this is due to central laboratory error (after Sponsor approval).

[d] If genotype screening results are available earlier, Screening Stage 2 can start before Day -14.

[e] COVID-19 RT-PCR testing: two PCR tests should be performed within approximately 36 hours (a second PCR would be performed only if the first results are negative).

[f] INR results should be available within 24 hours (and for the sample taken on Day 21, before cocktail administration on Day 22).

[g] Neutralizing antibodies will be tested in samples that were positive for OKZ antibodies.

[h] Sample may be taken at the local laboratory or another designated sample collection area.

8.1 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Table 3).

8.1.1 Physical Examinations

- A complete physical examination will include the evaluation of general appearance, skin, head, eyes, ears, nose, and throat, lymph nodes, respiratory, cardiovascular (CV), gastrointestinal (GI) including hepatobiliary assessment, musculoskeletal, endocrine system, neurological systems, and urogenital system.
- Physical examinations include but are not limited to respiratory infection symptoms (acute onset of cough, fever [oral temperature >37.5°C], dyspnea) and asked about contacts with suspected or confirmed COVID-19 cases/visiting areas where high frequency of COVID-19 are reported.
- All significant findings present at Screening must be reported in the relevant medical history/current medical conditions eCRF. Significant findings made after enrollment meeting the definition of an AE must be recorded in the AEs eCRF.

8.1.2 Vital Signs

- Body temperature, pulse rate, BP, and respiratory rate will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-supine position with a completely automated device. Manual techniques will only be used if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).
- At Screening, BP should be done in triplicate and the mean used to assess for subject eligibility.
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 BP measurement.

8.1.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals after the subject had been resting for at least 5 minutes in the semi-supine position and recorded in the eCRF.

8.1.4 Clinical Safety Laboratory Assessments

- The central laboratory will be used in this study to analyze routine blood samples. See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (see Table 3) for the timing and frequency.

- Results from the INR samples taken as safety assessments for warfarin (Days 2, 3, 4, 5, and 6, as well as Day 21, and Days 23, 24, 25, and 27) should be available within 24 hours (and for the sample taken on Day 21, before cocktail administration on Day 22).
- Subjects will be undergoing COVID-19 reverse transcription polymerase chain reaction (RT-PCR) testing. Two consecutive RT-PCR tests to be conducted within approximately 36 hours, the second RT-PCR test will only be performed if the first test results are negative. Only subjects with a negative COVID-19 RT-PCR test result may be included in the study. Two consecutive RT-PCR tests will occur at Day -35 (Stage 1) - only if the Investigator suspects possible COVID-19 infection, at Day -3, Day 5, Day 19 and Day 29 (EOT) - obligatory. If the Investigator suspects possible COVID-19 infection - on Day 43. Only subjects with a negative COVID-19 RT-PCR test result may be administered the study treatment on Day 8. The RT-PCR testing will be performed at local laboratories.
- A rapid test will be conducted for the COVID-19 IgG/IgM testing at Screening–Stage 1 - only if the Investigator suspects possible COVID-19 infection, prior to first inhouse period (Day -2) - obligatory. If the Investigator suspects possible COVID-19 infection - prior to dose administration on Day 8 or/and prior to second inhouse period (Day 19) or/and Day 43. The serology will be performed onsite.
- COVID-19 (SARS-CoV-2 infections) will be regarded as AEs and summarized as such.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF and classify according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease/subject's health status, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 77 days after the last dose of study treatment (Day 99 Safety Follow-up Visit) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor, ie, until 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.

    – If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    – All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA (Table 3).

- If laboratory values from nonprotocol-specified laboratory assessments require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.1.5 Tuberculosis Risk Questionnaire

The questionnaire "Tuberculosis Risk Questionnaire" (see Appendix 8) should be used as a source document. The questionnaire will be completed at Screening as noted in Table 3.

At the Screening Visit, if question No. 1 (Does the subject have currently active TB disease or a history of active TB disease) or question No. 2 (Has the subject been in close contact [ie, sharing the same household, or other enclosed environment, such as a social gathering place, workplace, or facility, for extended periods during the day] with an individual with active TB within the past 1.5 years) of the questionnaire "Tuberculosis Risk Questionnaire for Screening Visit" is answered "Yes" the subject is not allowed to enter the study (see exclusion criterion # 23, Section 5.2). 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.

8.2 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 and SAEs from the signing of the ICF until the final EOS telephonic follow-up visit (Day 161 ±10 days) at the timepoints specified in the SoA (see Table 3). 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 study treatment (cocktail, OKZ and OKZ + cocktail). 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. The detailed analysis plan for COVID-19 can be included in the Statistical Analysis Plan (SAP).

8.2.1 Severity

The severity of AEs will be characterized according to the CTCAE grades and definitions summarized in Table 10.

Table 10 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.

8.2.2 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 nontreatment-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 center staff is responsible for obtaining any missing information.

8.2.3 Eliciting Adverse Event Information

A consistent methodology of nondirective questioning should be adopted for eliciting AE information at all subject evaluation timepoints. 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?"

8.2.4 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 (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization.
    - Confirmed cases of active TB should be recorded and reported as SAEs.
    - Potential hepatotoxicity events that fulfill any of the following criteria should be recorded and reported as SAEs:
        - ALT >3 × ULN and total bilirubin >2 × ULN;
        - ALT >8 × ULN at any time, regardless of total bilirubin or accompanying symptoms;
        - ALT >5 × ULN for ≥2 weeks, regardless of total bilirubin or accompanying symptoms. The elevation should be continuous for ≥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 study treatment should be discussed on a case-by-case basis.

- ALT >3 × ULN, accompanied by symptoms which, as determined by the Investigator, are the result of hepatic injury (eg, 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 the Sponsor's designee through the end of the Safety Follow-Up period (ie, for a period of approximately 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 the Sponsor or their 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 and not within 30 days of an acute myocardial infarction (MI) within scenarios:

- Death witnessed and occurring without new or worsening symptoms.
- Death witnessed within 60 min of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI.
- Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator (ICD) review).
- Death after unsuccessful resuscitation from cardiac arrest (eg, ICD unresponsive sudden cardiac death, pulseless electrical activity arrest).
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology.
- Unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead without any evidence supporting a specific non- cardiovascular cause of death (information about the patient's clinical status preceding death should be provided if available).

Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤24 h before being found dead, sudden cardiac death should be recorded. 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 (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

8.2.5 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.

8.2.6 Reporting and Follow-up Requirements for Pregnancies

Pregnancy per se is not an AE except for the cases when it is reasonable to suppose that administration of the study product reduced efficacy of contraceptive methods. Congenital abnormalities or birth defects in children of study subjects are considered to be SAEs. Elective abortions, abortions for medical reasons, with sequelae as well as any serious pregnancy complications (including spontaneous abortions) should be recorded as SAEs. Planned abortions without sequelae are not AEs.

Pregnancy of the female subjects and partners of male subjects exposed to the study treatment will be recorded since the first study drug administration until the last study-related procedure. All pregnancy cases reported during the study (including pregnancies of female partners of the study subjects) should be duly recorded.

Female subjects of childbearing potential will be instructed through the ICF to immediately inform the Investigator if they become pregnant during the study and up to 6 months after the OKZ dosing. The same, male subjects will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study and up to 6 months after the OKZ dosing.

If a pregnancy is reported, the female subject must be immediately discontinued from the study and followed-up as described in the Section 7.2.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.

8.2.7 Reporting of Adverse Events

Study center 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. All AEs, whether reported by the subject or noted by study center 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, 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 the Sponsor's designee their assessment of the potential relatedness of each AE to protocol procedure and/or study treatment via the eCRF. Study center 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 the Sponsor's designee via eCRF, electronic data capture (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 (eg, 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 (ie, any procedure required by the study protocol). The action taken, and the outcome must also be recorded in the AE page of the eCRF.

8.2.8 Reporting of Serious Adverse Events

All SAEs that occur at or after Visit 1, regardless of the Investigator's assessment on causality, must be recorded on the relevant pages of the eCRF and reported to the Sponsor 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, and the timelines and procedure for follow-up reports are the same as those for the initial report. The Sponsor's designee is responsible for managing the safety database.

The Sponsor 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 the Sponsor's designee through the end of the Safety Follow-Up period (ie, 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.

8.2.9 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

The Sponsor'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 the Sponsor'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. The Sponsor'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 center 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.

8.2.10 Follow-up of Adverse Events

Any AEs that occur at or after Visit 1 until the end of the Safety Follow-Up period (ie, 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, the Sponsor or its designee must concur with the Investigator's assessment.

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

8.3 Disease Activity Assessments

The disease activity will be assessed by Patient Global Assessment of Disease Activity (Visual Analog Scale – Bullet Scale) and Disease Activity Score 28-Joint Count (C-Reactive Protein) – DAS28 (CRP).

8.3.1 Patient Global Assessment of Disease Activity (Visual Analog Scale – Bullet Scale)

Subjects will assess their overall disease activity using a visual analog scale (VAS) bullet scale of 21 circles in 0.5-unit increments, numbered below each circle, where 0 is "very well" and 10 is "very poorly", 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.

See Appendix 9 for more details.

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

The DAS28 (CRP) will be calculated using the Swollen Joint Count (SJC) (28 joints), Tender Joint Count (TJC) (28 joints), CRP level (mg/dL), and the Patient Global Assessment of Disease Activity (VAS) according to the following formula:

DAS28 (CRP) = 0.56 × √(TJC) + 0.28 × √(SJC) + 0.36 × lognat (CRP + 1) + 0.14 × Patient Global Assessment of Disease Activity (VAS) + 0.96

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

- Shoulders, elbows, wrists, and knees, and for each hand: interphalangeal joint (IP) on digit 1, proximal interphalangeal joints (PIP) on digits 2 to 5, and metacarpophalangeal joints (MCP) on digits 1 to 5 (See Appendix 9 for more details).

8.4 Pharmacokinetics

8.4.1 Collection of Samples

- Venous blood samples (main and back-up) will be collected for measurement of plasma concentrations of study treatment and cocktail substrates at times as specified in the SoA (see Table 3, Table 4, and Table 5). Blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. The actual date and time (24-hour clock time) of each sample will be recorded in the source documents. The time and date of study treatment administration will also be recorded in the source documents. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.
- Predose samples may be collected within 30 minutes before dose administration. A 2-minute window will be allowed for samples taken up to 30 minutes postdose; a 5-minute window will be allowed for samples taken at 1 to 30 hours postdose; a 2-hour window for samples taken at 48 hours to 120 hours postdose; and a +1-calendar day window is allowed for the 168-hour postdose sample.

8.4.2 Determination of Drug Concentration

- Samples for the determination of study treatment and cocktail substrates in plasma will be analyzed using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.
- All samples still within the known stability of the analyte of interest at the time of receipt by the bioanalytical laboratory will be analyzed.
- Remaining plasma samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays. Samples collected for analyses of study treatment and cocktail substrates plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

- A single blood sample or separate samples may be taken at shared timepoints as described in the Laboratory Manual.

8.4.3 Calculation of Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.0 or higher (Certara, L.P. Princeton, New Jersey, United States of America [USA]) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from dosing will be used for the final plasma PK parameter calculations.

Plasma Blood Pharmacokinetic Parameters

The PK parameters in Table 11 will be determined for the cocktail substrates, when possible.

Table 11 Plasma Blood Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Maximum concentration obtained directly from the observed concentration versus time data
t_{max}	Time to C_{max}
$AUC_{(0\text{-inf})}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
CL/F	Apparent oral plasma clearance
V_z/F	Apparent volume of distribution
$t_{1/2}$	Terminal half-life; a minimum of 3 points will be used for estimation
λ_z	Terminal rate constant

Additional plasma parameters may be calculated if deemed appropriate.

8.5 Pharmacodynamics

Venous blood samples will be collected for measurement of IL-6 and CRP at the timepoints specified below.

Blood sampling for the measurement of IL-6 and CRP will be performed. IL-6 and CRP levels will be measured at Screening, prior to dosing with the cocktail on Day 1, prior to dose administration with OKZ on Day 8, and post OKZ dose administration on Day 9, Day 15, Day 22 (prior to dose administration of the cocktail on Day 22), and Day 29, which will be considered the EOT Visit.

8.6 Genetics

Blood samples for DNA isolation will be collected from subjects who have consented to the study to identify intermediate metabolizers of CYP2C9 (genotype *1/*2,*1/*3), poor metabolizers of CYP2C9 (genotype *2/*2, 2/*3,*3/*3) or CYP2C19 (genotype *2/*2,*2/*3, *3/*3), ultra-rapid metabolizers of CYP2C19 (*17/*17), or high sensitivity to warfarin (VKORCI genotype AG and AA). Additional blood sampling for future genotype testing to identify any genotypes that could have significant impact on CYP metabolism but not listed above will also be performed.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 7 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study Reference Manual.

8.7 Immunogenicity Assessments

Antibodies to OKZ will be evaluated in plasma samples collected from all subjects according to the SoA. Additionally, plasma samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to OKZ and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to OKZ and/or further characterize the immunogenicity of OKZ. Neutralizing antibodies will be tested in samples that were positive for OKZ antibodies.

The detection and characterization of antibodies to OKZ will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to OKZ will also be evaluated for OKZ plasma concentration to enable interpretation of the antibody data. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject’s last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to OKZ.

8.8 Health Economics/Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

All statistical analyses will be performed using SAS® Version 9.4 or later.

9.1 Statistical Hypotheses

The assessment of the effect of OKZ on the PK of the probe substrates, caffeine, S-warfarin, omeprazole, and midazolam will be undertaken using descriptive statistics of the PK parameters listed in Table 11 at each of the relevant timepoints listed in Table 4. Additionally, estimates of the change after administration of OKZ in C_{max}, $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-last})}$ for each of these substrates will be analyzed.

9.2 Sample Size Determination

No historical data are available for the reduction in S-warfarin $AUC_{(0\text{-last})}$ following administration of OKZ. Hence, the following sample size computation is based on results reported for another compound (sirukumab) in the same class of medications as OKZ. Zhuang et al, 2015, reported an 18% (90% confidence interval [CI]: 0.73 to 0.92), 18% (90% CI: 0.73 to 0.92), and 19% (90% CI: 0.72 to 0.91) reduction in S-warfarin $AUC_{(0\text{-inf})}$ at 1, 3, and 6 weeks, respectively, following sirukumab administration in 12 subjects with RA. Assuming a dropout rate of 20%, approximately 15 subjects who meet the study eligibility criteria should be enrolled so that 12 evaluable subjects complete the study. However, if necessary, additional subjects may be dosed to obtain the 12 evaluable subjects required. This sample size (ie, 12 evaluable subjects) will have over 95% power to determine whether a 90% CI of the S-warfarin $AUC_{(0\text{-last})}$ ratio of the geometric mean for some timepoint after the administration of OKZ to that before OKZ administration is within the interval 80% to 125%. The power was calculated assuming a 13% coefficient of variation (CV) for S-warfarin $AUC_{(0\text{-last})}$.

Similarly, no historical data are available for the reduction in midazolam and omeprazole $AUC_{(0\text{-inf})}$ following administration of OKZ. Based on Zhuang et al, 2015, a sample size of 12 subjects with RA was sufficient to describe the effect of sirukumab on the model substrates midazolam and omeprazole with a reduction in $AUC_{(0\text{-inf})}$ of 30% (90% CI: 0.51 to 0.96) to 35% (90% CI: 0.47 to 0.89) and 37% (90% CI: 0.36 to 1.09) to 45% (90% CI: 0.32 to 0.96), respectively following sirukumab administration in 12 subjects with RA. Similarly, the effect of tocilizumab infusion on simvastatin and omeprazole exposure was well described with 8 subjects (28% reduction in omeprazole $AUC_{(0\text{-inf})}$) (Zhou and Meibohm, 2013). No statistical powering or formal comparisons are planned for midazolam and omeprazole substrates.

Caffeine is included in this study to further evaluate the effect of CYP450 modulators on this isozyme in subjects with RA. Again, no historical data are available for the reduction in caffeine $AUC_{(0\text{-inf})}$ following administration of OKZ. As per Zhuang et al (2015) (Zhuang et al, 2015), caffeine $AUC_{(0\text{-inf})}$ was increased by 20% (90% CI: 0.75 to 1.91) to 34% (90% CI: 0.84 to 2.15)

following sirukumab administration in 12 subjects with RA. This study is not powered to detect treatment differences in caffeine.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 12 are defined.

Table 12 Analysis Sets

Analysis Set	Description
Screened Analysis Set	All subjects who sign the Informed Consent Form (ICF).
Enrolled Analysis Set	All subjects who signed the ICF and were deemed as meeting all eligibility criteria by the Investigator prior to their first dose of study treatment.
Safety Analysis Set	The Safety population will include all subjects who receive at least 1 dose of study treatment (CYP450 probe cocktail or olokizumab [OKZ]). Subjects will be analyzed according to the treatment they received.
Pharmacokinetic (PK) Analysis Set	The PK population will include all subjects who receive at least 1 dose of study treatment (cocktail or OKZ) and who have at least 1 quantifiable plasma concentration for any of the cocktail drugs or OKZ collected postdose without protocol deviations or events that could affect those concentrations. The list of protocol deviations or events that could affect the plasma concentrations will be finalized before the database lock from the list of all protocol deviations that occurred during the study.
Pharmacodynamic (PD) Analysis Set	The PD population will include all subjects who receive at least 1 dose of study treatment (cocktail or OKZ) and who have at least 1 PD endpoint collected after cocktail or OKZ administration without protocol deviations or events that could affect those endpoints. The list of protocol deviations or events that could affect the PD endpoints will be finalized before the database lock from the list of all protocol deviations that will occurred during the study.

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size [n], mean, standard deviation [SD], median, minimum [min], and maximum [max];
- Categorical variables: frequencies and percentages.

Individual subject data will be presented in listings.

9.4.1 Disease Activity Analysis

Descriptive statistics for change from baseline in Disease Activity Score 28 joint count (DAS28) and Patient Global Assessment of Disease Activity (Bullet Scale) will be presented.

9.4.2 Pharmacokinetic/Pharmacodynamic Analyses

9.4.2.1 Pharmacokinetic Analyses

The PK analyses will be based on the Pharmacokinetic Analysis Set.

Concentrations and PK parameters for the cocktail drugs (caffeine, S-warfarin, omeprazole, and midazolam), and OKZ (concentration only) in plasma will be summarized using descriptive statistics. Geometric mean and CV will also be provided.

The natural log transformed PK parameters (C_{max}, $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-last})}$) of each cocktail substrate will be analyzed using a linear mixed effects model with a fixed effect for treatment and a random effect for subject. Estimates of the mean difference between treatments (OKZ + cocktail substrate compared to cocktail substrate alone) and its corresponding 90% CIs will be calculated. The mean differences and the CIs will be back transformed to the original scale to obtain estimates of the geometric mean ratios and the associated 90% CIs.

Interpretation of the results will be based on the size of the estimated geometric mean ratios and 90% CIs.

PK parameters can be calculated for part/all patients preliminary that will be documented accordingly in analysis plan.

9.4.2.2 Pharmacodynamic Analyses

Descriptive statistic of IL-6 and CRP concentrations and their change from baseline (CFB) concentration values will be listed and summarized by scheduled collection time. Line plots of mean concentrations over time will also be presented.

Interleukin-6 (IL-6) and CRP concentrations descriptive statistics will be presented by the visits at which they are scheduled to be collected as shown in the SoA. By-subject listings showing each subject's observed values in order by Study Day will also be provided.

9.4.3 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

All safety data including any AEs, AEs with an outcome of death, SAEs, AEs leading to discontinuation of study treatment, 12-lead ECG, vital signs, physical examination results and laboratory assessments will be listed by subject and within subject by start date or where relevant assessment date.

All AEs will be mapped to SOC and PT using MedDRA Version 20.0 or higher.

The number and percentage of subjects with TEAEs, SAEs and TEAs leading to study discontinuation will be summarized separately by MedDRA SOC and PT without regard to severity or relationship to study treatment.

A table summarizing TEAE by severity will be produced. The table will display the number and percentage of subjects with TEAEs summarized by MedDRA SOC, PT, and maximum severity.

A table summarizing TEAE by relationship to OKZ will be produced. This table will display the number and percentage of subjects with TEAEs summarized by MedDRA SOC, PT, and maximum relationship to study drug. A similar table summarizing TEAEs by maximum relationship to the cocktail will be produced.

For Period 1, assessment of relationship will automatically be between the cocktail and AE. For Period 2, assessment of relationship will automatically be between the OKZ and AE. For Period 3, assessment of relationship between study treatment and AE should be done separately for OKZ and the cocktail (2 questions in the eCRF: 1 for the relationship to OKZ and 1 for the relationship to the cocktail).

All weight, BMI and vital signs measurements, 12-lead ECG results, and laboratory test results will be summarized using descriptive statistics at each visit for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign, and ECG values will also be summarized using descriptive statistics

The number and percentage of subjects testing positive for ADAs will be summarized over time. A listing will be presented for COVID-19 positive cases reported. The detailed analysis plan for COVID-19 can be included in the SAP.

9.4.4 Other Analyses

A table showing the number and percentage of subjects who had each medical history condition coded to MedDRA Version 20.0 or higher SOC and PT and a by-subject data listing with each subject's conditions in order by start date will be presented.

Descriptive statistics and a by-subject listings will also be presented for demographic characteristics, subject disposition, analysis set, prior, and concomitant medications, disease history, and exposure to each study treatment.

9.4.5 Missing Data

Missing study treatment data will not be imputed. Rules for imputing missing dates will be described in the SAP.

9.5 Interim Analyses

Interim analysis of the data collected after the last End of treatment visit of the last patient in the study can be conducted.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
λ_z	Terminal rate constant
ACR	American College of Rheumatology
ADA	Antidrug antibody(ies)
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-inf})}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation
BP	Blood pressure
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CL/F	Apparent oral plasma clearance
C_{max}	Maximum concentration obtained directly from the observed concentration versus time data
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CV	Coefficient of variation
CYP	Cytochrome P450 isozyme
DAS28	Disease Activity Score 28 joint count
DMARDs	Disease modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
ECD	Electronic data capture
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment
FSH	Follicle-stimulating hormone

Abbreviation	Definition
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
HB	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICD	Implantable Cardioverter-Defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGRA	Interferon-gamma release assay
IL-6	Interleukin-6
IRB	Institutional Review Board
mAb	Monoclonal atibody
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
Min	Minimum
MTX	Methotrexate
NTCP	Sodium/taurocholate cotransporting polypeptide
OKZ	Olokizumab
PD	Pharmacodynamic
PK	Pharmacokinetic
q2w	Every 2 weeks
q4w	Every 4 weeks
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDAI	Simplified Disease Activity Index
SFU	Safety Follow-up
SoA	Schedule of Activities
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor alpha
TNFi	TNF-α inhibitor
$t_{1/2}$	Terminal half-life
t_{max}	Time to C_{max}
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution
VKORC1	Vitamin K epOxide Reductase Complex subunit 1
WOCBP	Woman of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines Revision 2.
  - Applicable laws and regulations.
  - Order No. 200n dated April 01, 2016 of the Ministry of Health of the Russian Federation on Approval of Rules for Good Clinical Practice.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 11). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement

procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor 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.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 14 days from the previous ICF signature date and there have been no changes to the ICF previously signed by the subject.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- 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.
- The Sponsor or its representative will not provide individual genotype 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.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

No safety review committee will be initiated for this study.

Table 13 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Site Monitoring Medical Monitoring	CRO/3rd party
Study Master File	CRO
Data Management	CRO/3rd party
Clinical Supply Management	Sponsor/3rd party
Quality Assurance Auditing	Sponsor/CRO/3rd party
Biostatistics Medical Writing	CRO
Laboratory Assessments	3rd party
Electrocardiogram Collection, Review, and Analysis	3rd party
Bioanalytical Sample Analysis	3rd party
Pharmacokinetic Analysis	CRO

CRO = Contract Research Organization

Medical Monitor

The Medical Monitor will be identified and employed before the start of the Study.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database (EudraCT) a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All subject data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study center data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation or if local laboratory tests are required by the protocol. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet Count	White Blood Cell Count with Differential
	Red Blood Cell Count	Hematocrit
	Hemoglobin	
Clinical Chemistry[a]	Creatinine	Aspartate aminotransferase (AST)
	Glucose (fasting)	Alanine aminotransferase (ALT)
	Sodium	Alkaline phosphatase (ALP)
	Gamma glutamyl transferase (GGT)	Creatine kinase
	Total bilirubin	Potassium
	Total protein	Direct and indirect bilirubin
	Total cholesterol	Albumin
Biomarkers	C-reactive protein	Interleukin-6
Coagulation	International normalized ratio (INR)[b]	Activated partial thromboplastin time (aPTT)
		Fibrinogen
Urinalysis	Leucocytes	Red blood cells
	Protein	pH
	Bilirubin	Nitrite
	Urobilinogen	Specific gravity
	Ketones	Glucose
	Microscopy (if clinically indicated)	
Viral serology	HIV I and II	Hepatitis C Virus
	HBsAg	anti-HBs
	anti-HBc	HBV DNA[b]

Laboratory Assessments	Parameters	
Drugs of abuse and alcohol[c]	Amphetamine/Metamphetamine	Opiates/Opioids
	Ethanol	Benzodiazepines
	Marijuana	Methadone/Methadone metabolite
	Cocaine	Barbiturates
	Ketamine	Ecstasy (3,4-Methylenedioxymethamphetamine)
	Cotinine	Phencyclidine
	Tricyclin anti-depressants (TCA)	
Glycosylated hemoglobin	HbA1c	
SARS-CoV-2 screening	Anti-SARS-CoV-2 IgM	
	Anti-SARS-CoV-2 IgG	
	SARS-CoV-2 (RT-PCR)	
Other screening tests	QuantiFERON-TB Gold Plus interferon-gamma release assay (IGRA).	
	Follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only).	
	Human Chorionic Gonadotropin (HCG) blood (serum_ test (as needed for women of childbearing potential at Screening).	
	Human Chorionic Gonadotropin (HCG) urine test (as needed for women of childbearing potential at further visits).	
	CYP2C9, CYP2C19 and high sensitivity to warfarin genotyping.	
	All study-required laboratory assessments will be performed by the central laboratory.	

Abbreviations: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; DNA = deoxyribonucleic acid; eCRF = electronic case report form; HbA_{1c} = glycosylated hemoglobin A_{1c}; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis.

NOTES:

[a] The following laboratory abnormalities require prompt retesting after the initial abnormal result is reported to the study center (within 72 hours of receiving abnormal liver function test [LFT] results and within 5 days of receiving all other abnormal results):

- Any single ALT and/or AST elevation >3 × upper limit of normal (ULN), regardless of total bilirubin (repeat laboratory testing must include total bilirubin, direct and indirect bilirubin, GGT, INR, ALP, creatine kinase, and hematology assessment)
- Neutrophil count <1,000 × 10^6/L (<1,000/mm^3)
- Lymphocyte count <500 × 10^6/L (<500/mm^3)
- Platelet count <100,000 platelets/mm^3
- Any single hemoglobin value <8.0 g/dL or one that drops ≥20 g/L (2 g/dL) below baseline

[b] HBV DNA test to be performed in anti-HBc positive subjects only.

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.

Laboratory Assessments	Parameters
[b]	The results from INR samples taken as safety assessments for warfarin (Days 2, 3, 4, 5, and 6, as well as Day 21, and Days 23, 24, 25, and 27) should be available within 24 hours (and for the sample taken on Day 21, before cocktail administration on Day 22).
[c]	Urine and breath express tests can be performed at the study center using kits provided by the central laboratory.

Investigators must document their review of each laboratory safety report.

Appendix 4 Concomitant and Excluded Medications/Therapy

Concomitant Medication

Must have received MTX, sulfasalazine, or hydroxychloroquine for at least 12 weeks prior to Day 1 and in stable dose for at least 6 weeks prior to Day 1 without significant AEs. Stable doses of MTX should be 10 mg to 25 mg weekly with folic acid (at least 5 mg weekly or equivalent). No significant side effects based on the Investigator's judgment should be observed during treatment by these agents. The maximum allowed doses of sulfasalazine and hydroxychloroquine are:

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

Note: The doses should remain stable and not be changed from the time of signing the ICF until the end of the treatment period (EOT, Day 29).

Restricted and Excluded Medication

Excluded medications/therapy is listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

As per the exclusion criteria (Section 5.2), the following medications/therapy are not allowed within the mentioned time frame:

Medications	Restrictions
DMARDs	
Azathioprine, cyclosporine, chloroquine, gold, penicillamine, minocycline, or doxycycline	Restricted within 4 weeks of Day 1 and during the study
Leflunomide alone	Restricted within 12 weeks of Day 1 and during the study
Leflunomide with elimination procedure with cholestyramine at a dosage of 8 grams 3 times daily for at least 24 hours	Restricted within 4 weeks of Day 1 and during the study
Leflunomide with elimination procedure with activated charcoal at a dosage of 50 grams 4 times a day for at least 24 hours	Restricted within 4 weeks of Day 1 and during the study
Cyclophosphamide	Restricted within 24 weeks of Day 1 and during the study
Treatment with any cell depleting therapies	
Anticluster of differentiation (CD)20 or investigational agents (eg, CAMPATH®, anti-CD4, anti-CD5, anti-CD3, and anti-CD19)	Not allowed during the study
Rituximab	Not allowed within 6 months of Day 1 and during the study

Treatment with tumor necrosis factor inhibitors or any other biologic therapy for the treatment of RA	Not allowed within 12 weeks of Day 1 and during the study
Parenteral and/or intra-articular or topical glucocorticoids	Restricted within 4 weeks prior to Day 1 and during the study
Oral glucocorticoids greater than 10 mg/day prednisone (or equivalent)	May not be used, or the dose changed within 4 weeks prior to Day 1 and during the study
NSAIDs	
Indomethacin and ketorolac	Not allowed during the study
Other NSAIDs	Must be taken at a stable dose and route of administration for at least 2 weeks prior to Day 1 and during the study
Hormone replacement therapy	Restricted within 4 weeks prior to Day 1 and during the study
Vaccination with live vaccines	Restricted within 6 weeks prior to Day 1 and during the study
Use of aspirin or other antiplatelet agents and anticoagulants including warfarin	Restricted within 4 weeks prior to Day 1 and during the study
Use of any prescription or nonprescription drugs or other products (eg, herbal preparations, food products) known to be inhibitors/inducers of CYP3A4, CYP2C9, CYP2C19, or CYP1A2 otherwise not mentioned above	Restricted within 4 weeks prior to Day 1 and during the study. See Table 15 for a detailed list of these compounds
Use of any other herbal preparations (including foods or beverages containing herbal preparations), dietary supplements, or natural medications	Restricted within 14 days prior to Day 1 and during the study
Midazolam and/or omeprazole (or esomeprazole)	Restricted within 14 days prior to Day 1 and during the study
Consumption of any caffeine-containing drinks or food, eg, coffee, tea, chocolate, caffeine-containing energy drinks (eg, Red Bull), or cola	Restricted within 48 hours prior to each administration of the cocktail (Day1 and Day 22)
Medication which could adversely affect gastrointestinal motility or transit (eg, diphenoxylate, [loperamide], metoclopramide, cisapride, tegaserod, erythromycin)	Restricted from 7 days prior to each administration of the cocktail drugs (Day 1 and Day 22) through the 48 hours following each cocktail administration

Table 15 List of Cytochrome P450 Inhibitors and Inducers

	CYP1A2	CYP2C9	CYP2C19	CYP3A4
Inhibitors	Amiodarone, efavirenz, fluoroquinolones, fluvoxamine, furafylline, interferon, methoxsalen, mibefradil, ticlopidine Strong inhibitors: Fluvoxamine, ciprofloxacin Weak inhibitors: Cimetidine	Efavirenz, fenofibrate, fluconazole, Fluvastatin, fluvoxamine, isoniazid, lovastatin, metronidazole, paroxetine, phenylbutazone, probenecid, sertraline, sulfamethoxazole, sulfaphenazole, teniposide, voriconazole, zafirlukast Strong inhibitors: Fluconazole Moderate inhibitors: Amiodarone	PPIs: Esomeprazole, lansoprazole, omeprazole, pantoprazole Other: Chloramphenicol, cimetidine, felbamate, fluoxetine, fluvoxamine, indomethacin, isoniazid, ketoconazole, modafinil, oral contraceptives, oxcarbazepine, probenecid, ticlopidine, topiramate, voriconazole	Amiodarone, chloramphenicol, boceprevir, ciprofloxacin, delaviridine, diethyl-dithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin Strong inhibitors: HIV Antivirals: Indinavir, nelfinavir, ritonavir Clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir Telithromycin Moderate inhibitors: Aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem Weak inhibitors: Cimetidine norfluoxetine starfruit telaprevir voriconazole

	CYP1A2	**CYP2C9**	**CYP2C19**	**CYP3A4**
Inducers	Broccoli, brussel sprouts, carbamazepine, char-grilled meat, insulin, methylcholanthrene, modafinil, nafcillin, beta-naphthoflavone, omeprazole, rifampin, tobacco	Carbamazepine, enzalutamide, nevirapine, phenobarbital, rifampin, secobarbital, St. John's Wort	Carbamazepine, efavirenz, enzalutamide, norethindrone, prednisone, rifampicin, ritonavir, St. John's Wort	HIV Antivirals: Efaviren, nevirapine Barbiturates, carbamazepine, enzalutamide, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, troglitazone

Abbreviations: CYP = Cytochrome P450 isozyme; HIV = Human immunodeficiency virus; PPI = proton-pump inhibitor
Source: https://drug-interactions.medicine.iu.edu/Main-Table.aspx

Appendix 5 Stages of Heart Failure – New York Heart Association Classification

The Stages of heart failure – New York Heart Association classification:

Class I (Mild)	No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnea
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little, Brown & Co; 1994:253-256.

Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile (i.e. of childbearing potential) following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the Following Categories Are Not Considered WOCBP

1. Female who is surgically sterile (ie, bilateral tubal ligation or removal of both ovaries and/or uterus at least 6 months prior to first dosing).
2. Female who is naturally postmenopausal (spontaneous cessation of menses) for at least 24 consecutive months prior to first dosing, with a follicle-stimulating hormone level at Screening of ≥40 mIU/mL.

Contraception Guidance

Female Subjects

- Female subjects defined at Screening as WOCBP are eligible to participate if they continue to have negative pregnancy test AND agree to use ONE of the highly effective contraception methods (see below) for duration of study (starting from signed ICF) and for 6 months after the OKZ dosing.

Highly Effective Contraceptive Methods for Female Subjects of Childbearing Potential are:

  - Total abstinence if it is the preferred and constant lifestyle of the subject. Thus, periodic abstinence such as ovulation, symptothermal, postovulation, calendar methods, and withdrawal are not acceptable methods of contraception.
  - Male sterilization surgery: at least 6 months prior to Screening (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). For female subjects, the vasectomized male should be the only partner.
  - Placement of established copper intrauterine device (IUD).

- Pregnant and breastfeeding women are not eligible to participate in this study.

Male Subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:

  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study (starting from signed ICF) and for 6 months after the OKZ dosing.
  - Agree to use a male condom and have their partner use of a contraceptive method with a failure rate of <1% per year (see below) when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study (starting from signed ICF) and for 6 months after the OKZ dosing.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for duration of study (starting from signed ICF) and for 6 months after the OKZ dosing.

Highly Effective Contraceptive Methods for Female Partners of Childbearing Potential

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 6 months after the last dose of study treatment.

Collection of Pregnancy Information

- The Investigator will attempt to collect pregnancy information (course and outcome) on any female subject of childbearing potential or male subject's female partner who becomes pregnant while the subject is in this study. This applies only to subjects who receive OKZ dosing.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy by submitting a Pregnancy Report via eCRF.
- The female study subjects are considered agreeable to allow follow-up on pregnancy by signing study ICF. 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. 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.
- The pregnant female subject or female partner of male subject will be followed to determine the outcome of the pregnancy. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.
- Once any additional information on pregnancy course and outcomes is obtained, the Investigator will update the Pregnancy Report in eCRF.
- Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Outcome of each pregnancy (spontaneous abortion, elective abortion or for medical reasons, normal delivery or delivery of a child with congenital abnormalities or birth defects) should be recorded even if the subject withdrew from the study.

Appendix 7 Genetics

Use/Analysis of DNA

- Genetic variation may impact a subject's response to study treatment, susceptibility to, and severity, and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.
- DNA samples will be used for research related to study treatment and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study treatment and/or treatments of this drug class and RA. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome.
- DNA samples will be analyzed for intermediate metabolizers of CYP2C9 (genotype *1/*2,*1/*3), poor metabolizers of CYP2C9 (genotype *2/*2, 2/*3; *3/*3) or CYP2C19 (genotype *2/*2, *3/*3), ultra-rapid metabolizers of CYP2C19 (*17/*17) or high sensitivity to warfarin (VKORCI genotype AG and AA). Additional blood sampling for genotype for the long-term storage will be performed. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the Clinical Study Report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study treatment or study treatments of this class or indication continues but no longer than 5 years or other period as per local requirements.

Appendix 8 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?	☐Yes ☐No
2) Has the subject been in close contact (ie, sharing the same household, or other enclosed environment, such as a social gathering place, workplace, or facility, for extended periods during the day) with an individual with active TB since the last scheduled visit?	☐Yes ☐No
3) Has the subject become an employee at a TB hospital, forensic medical examiner, or morgue since the last scheduled visit?	☐Yes ☐No
4) Has the subject started work or has the subject stayed in long-stay institutions (eg, homes for elderly or disabled, prisons, etc) since the last scheduled visit?	☐Yes ☐No
5) Does the subject reside in or is the subject frequently travelling to a TB endemic region? (as defined in Table 16) (only applicable for subjects not living in an endemic region)	☐Yes ☐No ☐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?	☐Yes ☐No
7) Does the subject have a new cough lasting more than 14 days or a change in a chronic cough?	☐Yes ☐No
8) Does the subject have night sweats?	☐Yes ☐No
9) Does the subject have a persistent fever?	☐Yes ☐No
10) Does the subject have unintentional weight loss (more than 10% of body weight) in the past 3 months?	☐Yes ☐No
11) Does the subject appear malnourished?	☐Yes ☐No
12) Has the subject had an abnormal chest X-ray since the last evaluation?	☐Yes ☐No

Physician's signature: _____

Table 16 List of Endemic TB Countries (Incidence >50/100,000)

Country	Incidence[a]	Country	Incidence[a]	Country	Incidence[a]
Afghanistan	189 (167–212)	Greenland	197 (173–223)	Nigeria	322 (189–488)
Algeria	78 (64–94)	Guatemala	57 (51–64)	Northern Mariana Islands	61 (53–69)
Angola	370 (240–529)	Guinea	177 (156–199)	Pakistan	270 (201–350)
Azerbaijan	77 (68–86)	Guinea-Bissau	369 (261–495)	Papua New Guinea	417 (304–547)
Bangladesh	227 (200–256)	Guyana	103 (91–116)	Peru	120 (98–145)
Belarus	58 (50–67)	Haiti	200 (177–225)	Philippines	288 (254–324)
Benin	61 (50–74)	India	167 (156–179)	Romania	81 (71–91)
Bhutan	164 (148–181)	Indonesia	399 (274–546)	Russia	84 (76–93)
Bolivia	120 (106–135)	Ivory Coast	165 (150–179)	Rwanda	63 (54–72)
Botswana	385 (361–410)	Kazakhstan	99 (64–141)	Sao Tome and Principe	97 (85–109)
Brunei	62 (54–70)	Kenya	246 (240–252)	Senegal	138 (122–154)
Burkina Faso	54 (48–59)	Kiribati	497 (406–597)	Sierra Leone	310 (235–394)
Burundi	126 (116–136)	Kyrgyzstan	142 (126–160)	Solomon Islands	86 (71–102)
Cabo Verde	138 (122–156)	Laos	189 (141–244)	Somalia	274 (242–308)
Cambodia	390 (353–428)	Lesotho	852 (612–1130)	South Africa	834 (737–936)
Cameroon	220 (195–247)	Liberia	308 (273–346)	South Korea	86 (81–91)
Central African Republic	375 (333–420)	Lithuania	62 (57–68)	South Sudan	146 (121–173)
Chad	159 (141–179)	Madagascar	235 (207–264)	Sri Lanka	65 (57–73)
China	68 (63–73)	Malawi	227 (122–365)	Sudan	94 (52–148)
China, Hong Kong	74 (65–84)	Malaysia	103 (83–124)	Swaziland	733 (533–963)
China, Macao	82 (72–93)	Mali	58 (56–59)	Tanzania	327 (155–561)
Congo	381 (335–430)	Marshall Islands	335 (274–402)	Tajikistan	91 (80–103)
Democratic Republic of Congo	325 (295–356)	Mauritania	111 (79–148)	Thailand	171 (90–276)

Country	Incidence[a]	Country	Incidence[a]	Country	Incidence[a]
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.

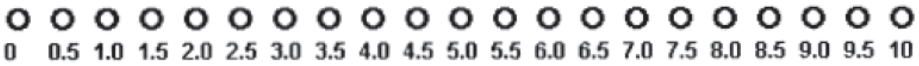
Appendix 9 DAS28 Joint Table

Left					Right				
Joint			Tender Joint?	Swollen Joint?	Joint			Tender Joint?	Swollen Joint?
Shoulder					Shoulder				
Elbow					Elbow				
Wrist					Wrist				
Knee					Knee				
Hand	Digit 1	IP			Hand	Digit 1	IP		
		MCP					MCP		
	Digit 2	PIP				Digit 2	PIP		
		MCP					MCP		
	Digit 3	PIP				Digit 3	PIP		
		MCP					MCP		
	Digit 4	PIP				Digit 4	PIP		
		MCP					MCP		
	Digit 5	PIP				Digit 5	PIP		
		MCP					MCP		

IP = Interphalangeal joint (IP) on digit 1; MCP = metacarpophalangeal joints on digits 1 to 5; PIP = proximal interphalangeal joints on digits 2 to 5.

Figure 2 Visual Analog Scale – Bullet Style

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, where 0 is “very well” and 10 is “very poorly”.



Appendix 10 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Appendix 11 Signature of Investigator

PROTOCOL TITLE: A Phase 1, Open-label, Study in Subjects with Rheumatoid Arthritis to Evaluate the Effect of a Single Dose of Olokizumab on the Pharmacokinetics of Substrates for CYP1A2, CYP2C9, CYP2C19, and CYP3A4

PROTOCOL NO: CL04041026

VERSION: Protocol Amendment 3

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 the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to CRO.

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 Center: _____

_____

_____