Title Page

Protocol Title:	A Phase 1, Randomized, Placebo-controlled, Double-blind, Multiple Ascending Dose Study to Investigate Safety, Tolerability, and Pharmacokinetics of Oral Doses of TCK-276 in Patients with Rheumatoid Arthritis
Brief Title:	A Study to Investigate Safety, Tolerability, and Pharmacokinetics of Oral Doses of TCK-276 in Patients with Rheumatoid Arthritis
Compound:	TCK-276
Indication:	Rheumatoid arthritis
Study Sponsor:	Teijin America, Inc. 1 Harbor Drive, Suite 200, Sausalito, CA, USA, 94965
Protocol Number:	TCK-276-102
Study Phase:	1
Regulatory Agency Identifying Number:	[redacted]
Version:	3.0
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Amendment Scope; Region/Country Identifier	Global
Approval Date:	Final, 12 Dec 2022
Date and Version of Previous Protocol:	[redacted]; Version: 2.0

Confidentiality Statement

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Sponsor Signatory:

[redacted]

Medical Monitor Name and Contact Information:

[redacted]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY			
Document	**Amendment Scope; Region/Country Identifier**	**Protocol Version**	**Date**
Amendment 2	Global	3.0	12 Dec 2022
Amendment 1	Global	2.0	[redacted]
Original Protocol	Global	1.0	[redacted]

Amendment 2 (12 Dec 2022)

Overall Rationale for the Amendment:

The original protocol was updated for the change of sentinel dosing approach for cohorts 2, 3, and 4. Editorial change was also made to correct internal inconsistencies related to patient identification card and to clarify the missing information on collection time of biomarker blood samples. A summary of changes is presented below.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.3.2 Benefit Assessment Section 4.1 Overall Design Section 6.1 Study Intervention(s) Administered	The sentences of sentinel dosing and Table 6-2 footnote 1 were modified to apply not for every cohort but only for cohort 1.	Results from nonclinical safety studies suggest that safety findings (such as hematological abnormality) with TCK-276 are not acute reactions and likely to be detected following longer-term administration. Based on the design of the study whereby the PK assessments occur only once the cohorts are fully enrolled and the current sentinel dosing would only be able to evaluate the short term Safety Assessments of TCK-276, subsequent sentinel dosing cohorts following cohort 1 were eliminated from this protocol.
Section 1.3 Schedule of Activities	Table 1-1 footnote 2 was updated to clarify that the biomarker samples need to be collected prior to dosing on Day 7.	Editorial change to clarify the missing information on sample collection time.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.2 Patient Identification Card	A sentence below was removed "The patient identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the Investigator is not available."	The statement was for the study where outpatients are enrolled. Emergency unblinding call center is not set up in the study. The patient identification card does not contain call center.

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1 Protocol Summary

1.1 Synopsis

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Brief Title: A Study to Investigate Safety, Tolerability, and Pharmacokinetics of Oral Doses of TCK-276 in Patients with Rheumatoid Arthritis

Sponsor Protocol No.: TCK-276-102

Study Phase: 1

Sponsor: Teijin America, Inc.

Rationale:

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and hyperplasia. Activated lymphocytes and macrophages produce various proinflammatory mediators which recruit synovial fibroblasts to the joint and activate them. Proliferation of activated synovial fibroblasts further increases production of proinflammatory mediators and tissue-degrading proteinase such as matrix metalloproteinase-3 (MMP-3), resulting in irreversible destruction of bone and cartilage. The current treatment approaches include conventional, biological, and targeted synthetic disease modifying antirheumatic drugs (DMARDs). However, a high proportion of patients only show a partial response or fail to respond to DMARDs currently on the market even used in combination. Therefore, there is a persistent unmet medical need for novel orally active agents with greater efficacy and equivalent or better safety with an alternative mechanism of action.

Teijin America, Inc., (hereafter referred to as Sponsor) has developed TCK-276 (Laboratory code number: TEI-T01276) as a novel synthetic DMARD with an alternative mechanism of action for the treatment of RA. The Sponsor has conducted the Phase 1 single ascending dose (SAD) study using an orally administered capsule containing 5 mg or 50 mg of TCK-276. The Sponsor thereafter plans to develop TCK-276 using an orally administered tablet containing 10 mg or 25 mg of TCK-276.

TCK-276 is a highly potent, orally active, and selective cyclin dependent kinase 4/6 (CDK4/6) inhibitor. Historically, CDK4/6 has been extensively explored as a target for anti-cancer therapeutics, however there is also mechanistic evidence to suggest that CDK4/6 contributes to

the pathogenesis of RA. Cyclin dependent kinase 4/6 is a key regulator at G1/S phase checkpoint in the cell cycle. Cyclin dependent kinase 4/6 forms a complex with D-type cyclins (CycD) and phosphorylates retinoblastoma protein (Rb), leading to depression of transcription factor E2F to accelerate S phase transition. Thus, inhibition of CDK4/6 leads to G1 arrest, and cell cycle progression is attenuated in synovial fibroblasts. In addition to the regulation of cell cycle, CDK4/6 has been reported to mediate the production of MMP-3 and monocyte chemoattractant protein 1 via Rb-independent and dependent pathways. Cyclin dependent kinase 4/6 likely contributes to the pathogenesis of RA by mediating the proliferation of synovial fibroblasts and the production of MMP-3. The inhibition of CDK4/6 may serve a useful therapeutic strategy for RA patients, particularly those with an inadequate response to existing DMARDs.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple oral doses of TCK 276 in patients with rheumatoid arthritis (RA)	• Safety and tolerability endpoints: The following safety and tolerability variables will be recorded at regular intervals during the study: o Vital signs measurements: supine blood pressure, pulse, body temperature, and respiratory rate o Cardiac safety for arrythmias, abnormalities including PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate (QTc) (Fridericia's correction [QTcF]) as assessed by 12-lead electrocardiogram (ECG) and cardiac telemetry o Incidence of laboratory abnormalities: hematology, clinical chemistry, coagulation, and urinalysis o Incidence and severity of adverse event (AE) and adverse event of special interest (AESI) (i.e., gastrointestinal toxicity and pulmonary symptoms indicative of interstitial lung disease) assessments o Physical examinations

Objectives	Endpoints
Secondary	
• To evaluate pharmacokinetic (PK) of TCK-276 and its metabolite (TEI-W00595) in patients with RA after multiple ascending dose (MAD) administration	• PK endpoints The following PK parameters for TCK-276 and TEI-W00595 will be determined, if calculable: ○ C_{max}: Maximum plasma concentration determined directly from the concentration-time profile (Days 1 and 7) ○ t_{max}: Time of maximum plasma concentration determined directly from the concentration-time profile (Days 1 and 7) ○ AUC_{tau}: Area under the plasma concentration-time curve over a dosing interval, tau = 24 hours (Days 1 and 7) ○ AUC_{0-t}: Area under the plasma concentration-time curve up to last measurable concentration (Days 1 and 7) ○ AUC_{0-inf}: Area under the plasma concentration-time curve from pre-dose (time 0) extrapolated to infinite time (Days 1 and 7) ○ MRT_{last}: Mean residence time up to last measurable concentration (Day 1 only) ○ MRT_{0-inf}: Mean residence time extrapolated to infinity (Days 1 and 7) ○ $t_{½}$: Terminal elimination half-life (Days 1 and 7) ○ CL/F: Apparent total body clearance (Days 1 and 7), determined for parent only ○ V_z/F: Apparent volume of distribution based on terminal phase (Days 1 and 7), determined for parent only ○ Metabolic ratio (MR) for C_{max}: Molar metabolic ratio of C_{max} calculated as (C_{max} [metabolite] × molecular weight of parent)/(C_{max} [parent] × molecular weight of metabolite) (Days 1 and 7)

Objectives	Endpoints
	○ MR for area under the plasma concentration-time curve (AUC): Molar metabolic ratio of AUC calculated as (AUC [metabolite] × molecular weight of parent)/(AUC [parent] × molecular weight of metabolite) (Days 1 and 7) ○ C_{trough}: Concentration in a dosing period defined as the pre-dose concentration of the day ○ R_{acc} (C_{max}): Accumulation ratio based on C_{max}: Calculated as C_{max} on Day 7/C_{max} on Day 1 ○ R_{acc} (AUC_{tau}): Accumulation ratio based on AUC_{tau}: Calculated as AUC_{tau} on Day 7/AUC_{tau} on Day 1 The following urinary PK parameters for TCK-276 will be determined in this study: ○ A_e: Amount of study drug excreted unchanged in the urine (Days 1 and 7) ○ F_e: Percentage of study drug excreted unchanged in the urine (Days 1 and 7) ○ CL_r: Renal clearance (Days 1 and 7) Other PK parameters will be determined if needed.
Exploratory	
• To evaluate the effect of TCK-276 on disease activity and biomarkers in patients with RA	• Exploratory endpoints The following exploratory disease activity parameters for RA will be assessed: ○ American College of Rheumatology (ACR) 20/50/70 response criteria ○ Disease activity score 28 (DAS28) ○ Clinical disease activity index (CDAI) ○ Simplified disease activity index (SDAI) The following exploratory biomarkers will be assessed: ○ Matrix metalloproteinase-3 (MMP-3) ○ Granulocyte macrophage colony-stimulating factor (GM-CSF)

Objectives	Endpoints
	○ C-X-C motif chemokine ligand 10 (CXCL10) ○ C-C motif chemokine ligand 2 (CCL2) ○ Cartilage oligomeric matrix protein (COMP) ○ Tumor necrosis factor (TNF)-alpha ○ TNF-R1 ○ Interleukin-6 (IL-6)

Overall Design:

This is a Phase 1, multi-center, double-blind, randomized, placebo-controlled, multiple ascending dose (MAD) study to evaluate the safety, tolerability, and pharmacokinetics (PK) of orally administered TCK-276 in both males and females with RA. Blood samples for possible future pharmacogenetic, possible future metabolite assessments, and possible future pharmacodynamic (PD) assessments will be collected.

A total of thirty-two (32) patients with RA will be enrolled in this clinical study. This MAD study will consist of 4 cohorts of 8 patients (6 active treatment and 2 matching placebo, or a 3:1 ratio), each receiving an oral dose of TCK-276 or matching placebo for 7 days (once daily [QD] under fed condition). The first cohort will be divided into 2 subgroups to implement the sentinel dosing approach. Within the cohort, the first subgroup will consist of 2 sentinel patients; one patient will receive TCK-276, and one patient will receive matching placebo. The second subgroup will consist of 6 patients (5 active treatment, 1 matching placebo). Individual patients in the second subgroup will be dosed at least 72 hours after the first dose of the second sentinel patient of the first subgroup following a decision by the Investigators based on all available safety data from the sentinel patients up to 48 hours post-dose. Subsequent cohorts (cohort 2-4) will not include the sentinel dosing approach.

Patients will be admitted to the site from the morning of Day -1 and sequestered for the duration of the treatment (dosing) period. Each patient will receive QD oral doses of either TCK-276 or matching placebo administered as tablets under fed condition in the morning of Day 1 to Day 7. The patients will be discharged on Day 10. The planned dose levels to be tested are 10 mg (Cohort 1), 25 mg (Cohort 2), 75 mg (Cohort 3), and 150 mg (Cohort 4) of TCK-276. Based on the results from the SAD study (5 mg to 185 mg dosing) and the projected clinical effective dose (i.e., 75 mg), 10 mg is selected as the starting dose level in the MAD study. The dose in Cohorts 2, 3, and 4 may be adjusted based on the safety and PK results from the previous cohorts, if necessary. The overall exposure to TCK-276 (in terms of geometric mean area under

the plasma concentration-time curve over a dosing interval [AUC_{tau}, tau = 24 hours]) on Day 7 would not be expected to exceed [redacted].

Dose escalation will only be allowed after blinded assessment of all safety, tolerability, and PK data up to Day 10 from each previous cohort evaluated by Investigators, Medical Monitor, and Sponsor representatives during the Safety Review Committee (SRC) meeting.

Brief Summary:

The purpose of this study is to evaluate the safety, tolerability, and PK of multiple orally administered TCK-276 in both males and females with RA.

Study details include:

- Study duration: approximately 42 days
- Treatment duration: Up to 11 days (Day -1 to Day 10)
- Visit frequency: Screening Visit, Days -1 to 10 Visits; Follow-up/end of treatment (EOT) Visit. Following discontinuation of TCK-276, patients will be followed unless they withdraw their informed consent for study participation.

Number of Patients:

A total of 32 patients with RA are planned for enrollment and randomized into 4 cohorts with 8 patients per cohort. Within each cohort, 6 patients will be randomized to TCK-276 and 2 patients will be randomized to matching placebo.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after Screening.

Intervention Groups and Duration:

This MAD study will consist of 4 cohorts of 8 patients (6 active treatment and 2 matching placebo, or a 3:1 ratio), each receiving an oral dose of TCK-276 or matching placebo for 7 days (QD under fed condition). The first cohort will be divided into 2 subgroups to implement the sentinel dosing approach. Within the cohort, the first subgroup will consist of 2 sentinel patients;

one patient will receive TCK-276, and one patient will receive matching placebo. The second subgroup will consist of 6 patients (5 active treatment, 1 matching placebo). Individual patients in the second subgroup will be dosed at least 72 hours after the first dose of the second sentinel patient of the first subgroup following a decision by the Investigators based on all available safety data from the sentinel patients up to 48 hours post-dose. Subsequent cohorts (cohort 2-4) will not include the sentinel dosing approach.

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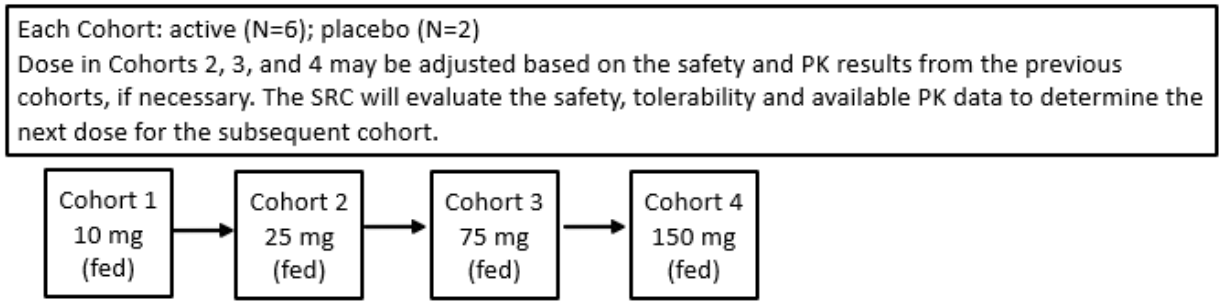
Dose Group	Treatment Assignment	
1	10 mg TCK-276 (N = 6)	Placebo (N = 2)
2	25 mg TCK-276 (N = 6)	Placebo (N = 2)
3	75 mg TCK-276 (N = 6)	Placebo (N = 2)
4	150 mg TCK-276 (N = 6)	Placebo (N = 2)

Data Monitoring/Other Committee:

A SRC will be appointed for this study. The SRC meeting will take place to review safety and PK data during each dose level. The SRC will evaluate the safety and tolerability data up to Follow-up/EOT Visit and available PK data up to Day 10 to determine the next dose for the subsequent cohort.

1.2 Schema

Figure 1–1 Study Design



N = number of patients; PK = pharmacokinetics; SRC = Safety Review Committee.

1.3 Schedule of Activities

Table 1-1 Schedule of Activities

Evaluation	Screening visit	Treatment period					Follow-up/ End of treatment	Early termination procedures
	Days							
	-28 to -2	-1	1	2-7	8, 9	10	14	
Informed consent	X							
Admission		X						
In-house stay		X	X	X	X	X		
Ambulatory visits	X						X	X
Discharge						X		
Inclusion/exclusion criteria	X	X	X					
Medical history	X	X						
Disease activity data (ACR20/50/70, DAS28, CDAI, SDAI)			X[1]	X[2]				
Blood sampling for ESR, assessed as part of disease activity data			X[1]	X[2]				
Demographics	X							
Weight and height (height only at Screening)	X	X				X		
Viral serology (HBsAG, anti-HBc, anti-HCV, anti-HIV)	X							
Drug, alcohol, and cotinine screen	X	X						
SARS-CoV-2 real time RT-PCR	X	X						
IGRA-TB test (Quantiferon)	X							
Chest X-ray	X							
Randomization			X					
Study drug administration			X	X				

Evaluation	Screening visit	Treatment period					Follow-up/ End of treatment	Early termination procedures
	Days							
	-28 to -2	-1	1	2-7	8, 9	10	14	
Urine pregnancy test (females)	X	X					X	X
FSH (post-menopausal females)	X							
Physical examination[3]	X	X				X	X	X
Clinical laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis)	X	X	X[1]	X[4]	X	X	X	X
Vital signs	X	X	X[5]	X	X	X	X	X
12-lead ECG[6]	X[6]	X[7]	X[8]	X[8]	X	X	X	X
Telemetry			X[9]	X[9]				
PK blood sampling[10]			X	X	X	X		
PK urine collection[11]			X	X	X	X		
Biomarker blood sampling			X[1]	X[2]				
Blood sampling for possible future pharmacogenetic assessments		X[12]						
Blood sampling for possible future metabolite assessments[10]			X	X	X	X		
Blood sampling for possible future PD assessments			X[1]	X[2]				
Prior/concomitant medications	X	X	X	X	X	X	X	X
AE monitoring[13]	X	X	X	X	X	X	X	X

ACR = American College of Rheumatology; AE = adverse event; CDAI = clinical disease activity index; DAS28 = disease activity score 28; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FSH = follicle stimulating hormone; HBc = hepatitis B core; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IGRA-TB = interferon gamma release assay for tuberculosis; PD = pharmacodynamic; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SDAI = simplified disease activity index.

1. Disease activity data (ACR20/50/70, DAS28, CDAI, SDAI, and blood sampling for ESR), blood for clinical laboratory tests, blood for biomarker assessments, and blood for possible future PD assessments will be collected prior to dosing on Day 1. Blood sampling for ESR will be collected and assessed at local laboratory.
2. Disease activity data (ACR20/50/70, DAS28, CDAI, SDAI, and blood sampling for ESR), blood for biomarker assessments, and blood for possible future PD assessments will be collected prior to dosing on Day 7 only. Blood sampling for ESR will be collected and assessed at local laboratory.
3. A full physical examination will be performed at the Screening Visit, Day 14, and Early termination visit; a brief physical will be performed on Days -1 and 10.
4. Blood for clinical laboratory tests will be withdrawn once on Days 4 and 7.
5. Vital signs will be collected at pre-dose and 1, 2, 4, 8, and 12 hours after dosing on Day 1.
6. 12-lead ECG will be conducted before blood sampling.
7. 12-lead ECG will be repeated once for eligibility confirmation at Screening and Day -1.
8. 12-lead ECG will be recorded at baseline and at 1, 2, 4, and 8 hours after dosing on Days 1 and 7.
9. Starting 2 hours prior to dosing and until 12 hours after dosing on Days 1 and 7.
10. Blood for PK sample analysis to determine parent and its metabolite concentrations and for possible future metabolite assessments will be sampled at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours (pre-dose of Day 2) after dosing on Day 1, pre-dose on Days 3, 4, 5, 6, and on 7 at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours after dosing on Day 7 (the sampling time points may be adjusted based on the PK results obtained from the previous parts or cohorts). The last dose will be administered on Day 7.
11. Urine for PK sample analysis will be collected at 0 (pre-dose) to 6, 6 to 12, and 12 to 24 hours after dosing on Day 1, and from 0 (pre-dose) to 6, 6 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after dosing on Day 7. Urine collection intervals may be adjusted based on the PK results obtained from the previous parts or cohorts, e.g., if plasma PK sampling times are adjusted, the urine sampling times will be updated.
12. Sample will be obtained only from patients that consent to pharmacogenomics sampling.
13. Any AEs occurring after the patient signs the ICF will be collected and monitored throughout the study via safety assessments, observation, and patient reporting.

2 Introduction

TCK-276 is a highly potent, orally active, and selective cyclin dependent kinase 4/6 (CDK4/6) inhibitor. The Sponsor is planning to develop TCK-276 as a novel synthetic disease modifying antirheumatic drug (DMARD) with an alternative mechanism of action for the treatment of rheumatoid arthritis (RA).

The term “study intervention” throughout the protocol, refers to TCK-276.

2.1 Study Rationale

Rheumatoid arthritis is an autoimmune disease characterized by synovial inflammation and hyperplasia. Activated lymphocytes and macrophages produce various proinflammatory mediators which recruit synovial fibroblasts to the joint and activate them. Proliferation of activated synovial fibroblasts further increases production of proinflammatory mediators and tissue-degrading proteinase such as matrix metalloproteinase-3 (MMP-3), resulting in irreversible destruction of bone and cartilage[1,2]. The current treatment approaches include conventional, biological, and targeted synthetic DMARDs. However, a high proportion of patients only show a partial response or fail to respond to DMARDs currently on the market even used in combination. Therefore, there is a persistent unmet medical need for novel orally active agents with greater efficacy and equivalent or better safety with an alternative mechanism of action.

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TCK-276 is a highly potent, orally active, and selective CDK4/6 inhibitor. Historically, CDK4/6 has been extensively explored as a target for anti-cancer therapeutics, however there is also mechanistic evidence to suggest that CDK4/6 contributes to the pathogenesis of RA[3]. Cyclin dependent kinase 4/6 is a key regulator at G1/S phase checkpoint in the cell cycle. Cyclin dependent kinase 4/6 forms a complex with D-type cyclins (CycD) and phosphorylates retinoblastoma protein (Rb), leading to depression of transcription factor E2F to accelerate S phase transition[3,4]. Thus, inhibition of CDK4/6 leads to G1 arrest, and cell cycle progression is attenuated in synovial fibroblasts[5]. In addition to the regulation of cell cycle, CDK4/6 has been reported to mediate the production of MMP-3 and monocyte chemoattractant protein 1 via

Rb-independent and dependent pathways[6]. Cyclin dependent kinase 4/6 likely contributes to the pathogenesis of RA by mediating the proliferation of synovial fibroblasts and the production of MMP-3. The inhibition of CDK4/6 may serve a useful therapeutic strategy for RA patients, particularly those with an inadequate response to existing DMARDs.

This multiple ascending dose (MAD) study will evaluate the safety, tolerability, and pharmacokinetic (PK) of orally administered TCK-276 in both male and female patients with RA.

The study is being conducted to establish a dose range that is well tolerated by the majority of study patients with RA and to provide exploratory data on the potential for the treatment of RA. The results of the clinical study will inform the design and dose selection of subsequent studies.

2.2 Background

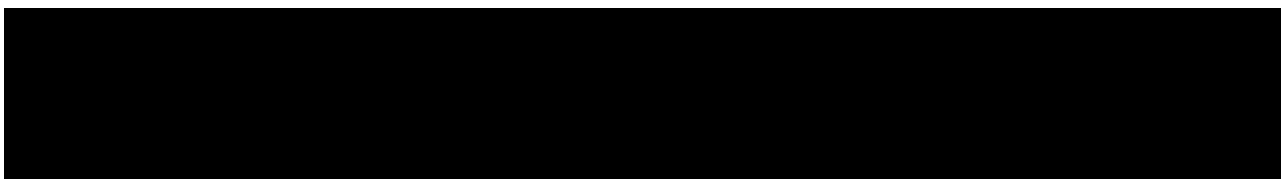
2.2.1 Summary of Findings from Non-clinical Studies with Potential Clinical Relevance

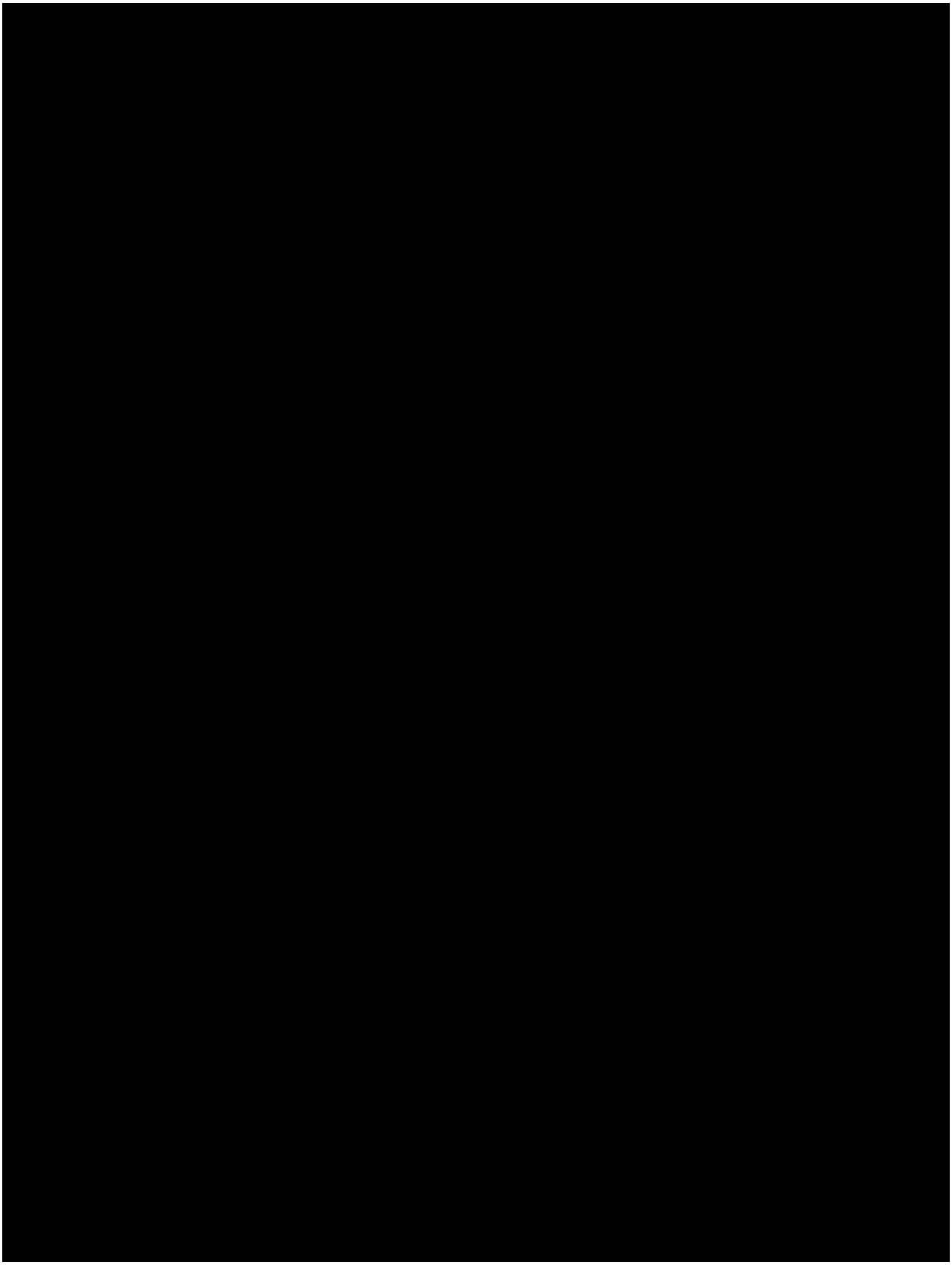
Pharmacodynamic (PD) studies demonstrated that TCK-276 inhibits CDK4/6 and has minimal potential for off-target kinase activity (Sections 5.1.1.2 and 5.1.2 of the Investigator's Brochure [IB][7]).

Results of *in vitro* pharmacology study using rheumatoid arthritis synovial fibroblasts (RASF) indicated that TCK-276 inhibited proliferation and MMP-3 production of RASF (Section 5.1.1.2.5 and 5.1.1.2.6 of the IB).

Results of *in vivo* pharmacology studies using rat and mouse arthritis models, indicated that TCK-276 at ≥ 15 mg/kg of tested doses was effective in the treatment of arthritis with no effect on bone marrow nucleated cells in rat arthritis model and TCK-276 at doses of ≥ 6.25 mg/kg was effective in the treatment of arthritis and bone destruction in mouse arthritis model (Sections 5.1.1.3.1 and 5.1.1.3.2 of the IB[7]).

Safety pharmacology studies were performed *in vitro* and *in vivo* (cardiovascular, central nervous, and respiratory systems) in rats and monkeys. No untoward effects were observed in these studies.





TCK-276 was not genotoxic based on the absence of mutagenic potential in bacterial reverse mutation, the absence of potential for inducing chromosomal aberration in human lymphocytes *in vitro* and in rat bone marrow *in vivo* (Section 5.3.3.2 of the IB[7]).

Embryo-fetal development studies have revealed evidence for teratogenicity in rats and rabbits and post-implantation loss (embryotoxicity) in rabbits (Section 5.3.5.3 of the IB[7]). In the male fertility study, there were no effects on the reproductive function of males or on early embryonic development when treated males were mated with untreated females (Section 5.3.5.1 of the IB[7]).

Based on the non-good laboratory practice preliminary phototoxicity study (non-good laboratory practice grade), TCK-276 is considered to have no phototoxic potential (Section 5.3.7.1 of the IB[7]).

In summary, the preclinical program supports the clinical development of TCK-276, as a once daily, self-administered, oral product for RA treatment. Collectively, the available data indicate that TCK-276 can be useful in the treatment of RA.

2.2.2 Summary of Findings from Previous Clinical Studies

The first-in-human (FIH) Phase 1 SAD study (Study TCK-276-101) evaluating TCK-276 has completed [redacted]; 48 subjects have been orally administered capsules ranging from 5 to 185 mg (geometric mean of $AUC_{0\text{-inf}}$: 39.7 to 2,260 ng·h/mL) once daily (QD). Clinical data from the SAD study of TCK-276 showed no drug-related safety signals (i.e., serious adverse events [SAEs], adverse events [AEs] leading to discontinuation). The plasma exposure levels for TCK-276 linearly increased following escalating TCK-276 administration with the proportion of metabolite (TEI-W00595) to parent remaining similar across dose levels. It was noted that no clinically meaningful differences in PK parameters were observed between fed or fasting states for either TCK-276 or its metabolite.

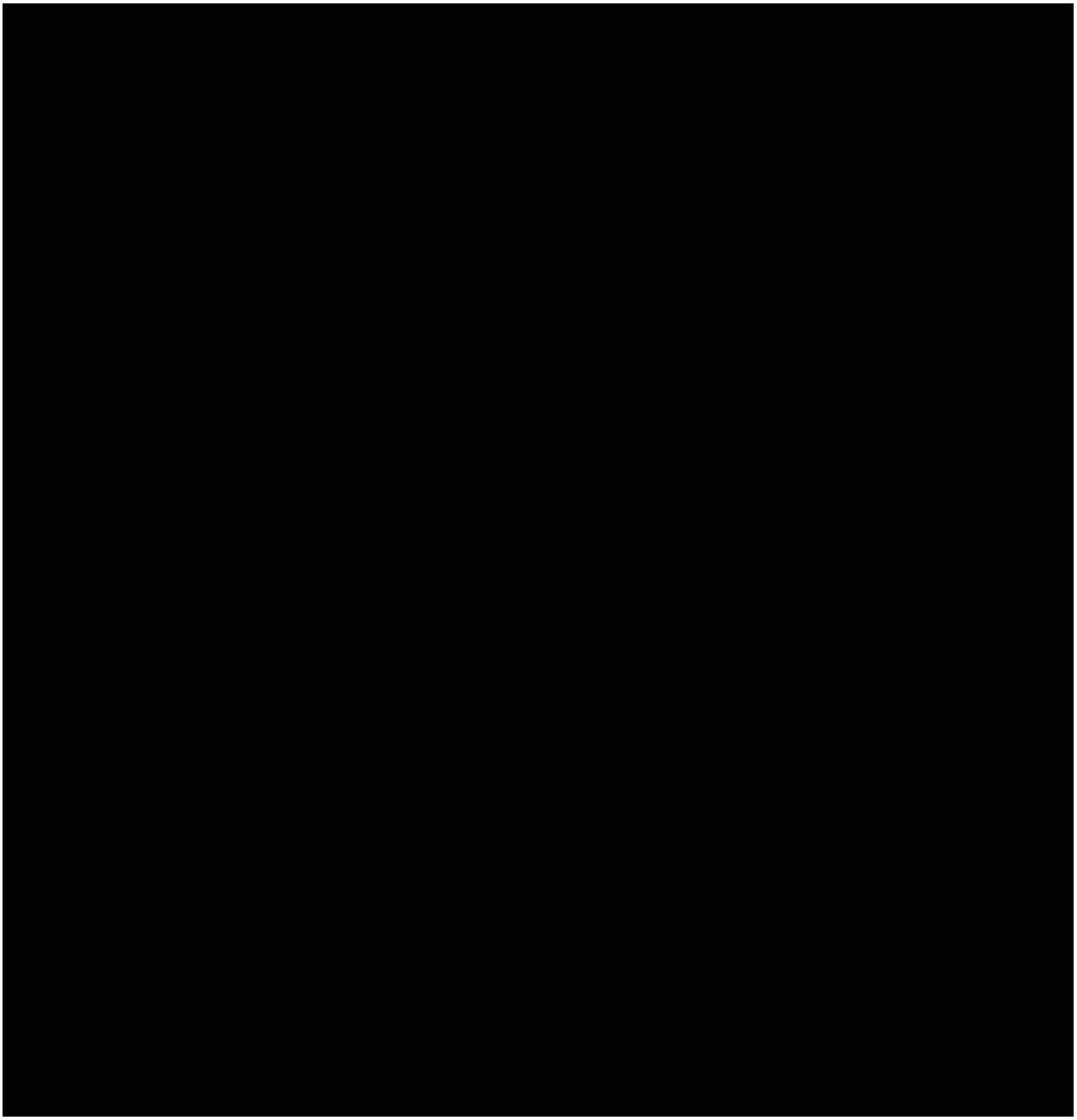
A detailed description of the chemistry, pharmacology, efficacy, and safety of TCK-276 is provided in the IB.

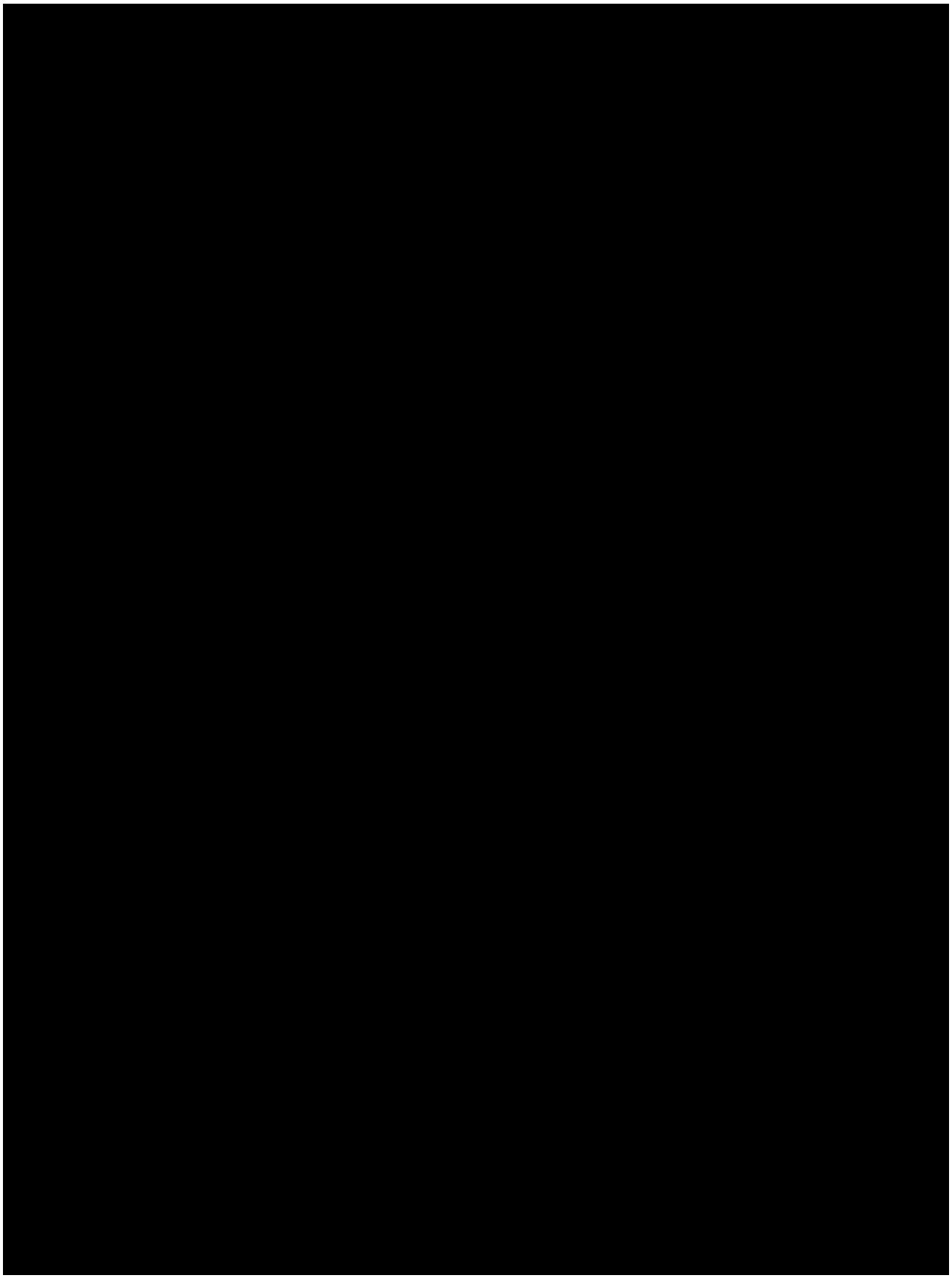
2.3 Benefit/Risk Assessment

The risks of TCK-276 known to date are outlined in Section 2.3.1 and the benefits are outlined in Section 2.3.2. More detailed information about the known and expected benefits and risks and reasonably expected AEs of TCK-276 can be found in the IB.

2.3.1 Risk Assessment

Table 2–1 Risk Assessment





[redacted]

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Risk of acquiring an infection with SARS-CoV-2 Risk of spreading a SARS-CoV-2 infection	• SARS-CoV-2 is known to be transmissible via respiratory droplets and any interventions that may potentially increase cough or aerosolization of respiratory secretions of an infected patient may increase risk of spread of disease.	• Described below this Table.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

There is currently an outbreak of respiratory disease (coronavirus disease 2019 [COVID-19]) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Food and Drug Administration (FDA)[8] have issued guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during the COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may be changed at a high pace. Given the circumstances of a potentially relapsing pandemic or epidemic situation regarding the spread of COVID-19 in the future, special attention will be paid to protect study patients and site staff involved in the investigations against infection with SARS-CoV-2.

The study intervention, TCK-276, may have the potential for CDK4/6 inhibition and the risk of causing immune suppression is low. Therefore, the risk the study patients to contract a COVID-19 infection will be similar to that of the general population. However, the risk of exposure to infected people cannot be completely excluded as the patients might be exposed in public areas (e.g., commute to the site following the treatment period) and have additional human contact (e.g., with site staff and other patients in the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- This study is going to start enrolling only when the Sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study. In addition, the study will not start until the local containment measures or other safety restrictions linked to the COVID-19 pandemic allow.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Patients will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat, fatigue, and changes of taste and smell throughout the study. Once clinical signs of infection are reported by patients, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on-site. If not, information on AEs and concomitant medications will be obtained via phone calls.
- Confirmation of COVID-19 infection by available approved laboratory standard testing should be conducted at Investigator's discretion. This would include serology testing at Screening and virus testing prior to any Admission.
- The probability of virus transmission will be controlled as much as possible by:
    - Advice for patients to adhere to local requirements for reduction of the public exposure while ambulatory.
    - Asking the potential patients to self-isolate for at least 5 days prior to admission.
    - Contacting patients by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs, and patients will be asked not to attend the site in case of suspected reports. In addition, patients will be asked about any contact with a person who has tested positive for SARS-CoV-2. If applicable, patients will be referred to the local health care system for further follow-up and treatment.
    - Physical distancing and person-to-person contact restrictions will be applied during site visits.
    - Where physical distancing is not possible, face shields will be used by study patients (surgical face mask, and gloves) and staff (for example but not limited to masks, gloves, protectors, and medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
    - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

- Patients will follow the site policy to mitigate the additional risks caused by COVID-19. All medical measures, risk/benefit, and restrictions associated with COVID-19 screening will be explained by the informed consent for COVID-19 screening, and written consent must be obtained before participating in the clinical study. Patients will be allowed to receive COVID-19 vaccines or boosters during the study period if necessary.

2.3.2 Benefit Assessment

TCK-276 is a highly potent, orally active, and selective CDK4/6 inhibitor as a novel synthetic DMARD with an alternative mechanism of action for the treatment of RA.

The protocol has been designed to minimize the risk to research patients. Patients will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. Sentinel dosing will be employed within the first cohort, and available safety/tolerability and PK data will be assessed after each dose level to determine if it is safe to escalate to the next planned higher dose.

Based on CDK4/6 inhibition mechanism of action, the adverse event of special interest (AESI) will be monitored as described in Section 2.3.1.

Given the safety and tolerability profile of TCK-276 in preclinical studies and the SAD study, also in view of the short treatment duration of 7 days, the overall risk to the patients in this study is deemed to be low and the patients cannot derive benefit from short term treatment. The study results will help to further develop TCK-276 as potential treatment for RA patients in future and will guide researchers to plan and design future studies. Therefore, the Sponsor considers that it is medically and ethically acceptable to perform the proposed study.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with TCK-276 are justified by the anticipated benefits that may be afforded to patients with RA.

3 Objectives and Endpoints

Study objectives and endpoints are summarized in Table 3–1.

Table 3–1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple oral doses of TCK 276 in patients with rheumatoid arthritis (RA)	• Safety and tolerability endpoints: The following safety and tolerability variables will be recorded at regular intervals during the study: ○ Vital signs measurements: supine blood pressure, pulse, body temperature, and respiratory rate ○ Cardiac safety for arrythmias, abnormalities including PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate (QTc) (Fridericia's correction [QTcF]) as assessed by 12-lead electrocardiogram (ECG) and cardiac telemetry ○ Incidence of laboratory abnormalities: hematology, clinical chemistry, coagulation, and urinalysis ○ Incidence and severity of adverse event (AE) and adverse event of special interest (AESI) (i.e., gastrointestinal toxicity and pulmonary symptoms indicative of interstitial lung disease) assessments ○ Physical examinations
Secondary	
• To evaluate pharmacokinetic (PK) of TCK-276 and its metabolite (TEI-W00595) in patients with RA after multiple ascending dose (MAD) administration	• PK endpoints The following PK parameters for TCK-276 and TEI-W00595 will be determined, if calculable: ○ C_{max}: Maximum plasma concentration determined directly from the concentration-time profile (Days 1 and 7)

Objectives	Endpoints
	○ t_{max}: Time of maximum plasma concentration determined directly from the concentration-time profile (Days 1 and 7) ○ AUC_{tau}: Area under the plasma concentration-time curve over a dosing interval, tau = 24 hours (Days 1 and 7) ○ AUC_{0-t}: Area under the plasma concentration-time curve up to last measurable concentration (Days 1 and 7) ○ AUC_{0-inf}: Area under the plasma concentration-time curve from pre-dose (time 0) extrapolated to infinite time (Days 1 and 7) ○ MRT_{last}: Mean residence time up to last measurable concentration (Day 1 only) ○ MRT_{0-inf}: Mean residence time extrapolated to infinity (Days 1 and 7) ○ $t_{½}$: Terminal elimination half-life (Days 1 and 7) ○ CL/F: Apparent total body clearance (Days 1 and 7), determined for parent only ○ V_z/F: Apparent volume of distribution based on terminal phase (Days 1 and 7), determined for parent only ○ Metabolic ratio (MR) for C_{max}: Molar metabolic ratio of C_{max} calculated as (C_{max} [metabolite] × molecular weight of parent)/(C_{max} [parent] × molecular weight of metabolite) (Days 1 and 7) ○ MR for area under the plasma concentration-time curve (AUC): Molar metabolic ratio of AUC calculated as (AUC [metabolite] × molecular weight of parent)/(AUC [parent] × molecular weight of metabolite) (Days 1 and 7) ○ C_{trough}: Concentration in a dosing period defined as the pre-dose concentration of the day

Objectives	Endpoints
	○ R_{acc} (C_{max}): Accumulation ratio based on C_{max}: Calculated as C_{max} on Day 7/C_{max} on Day 1 ○ R_{acc} (AUC_{tau}): Accumulation ratio based on AUC_{tau}: Calculated as AUC_{tau} on Day 7/AUC_{tau} on Day 1 The following urinary PK parameters for TCK-276 will be determined in this study: ○ A_e: Amount of study drug excreted unchanged in the urine (Days 1 and 7) ○ F_e: Percentage of study drug excreted unchanged in the urine (Days 1 and 7) ○ CL_r: Renal clearance (Days 1 and 7) Other PK parameters will be determined if needed.
Exploratory	
• To evaluate the effect of TCK-276 on disease activity and biomarkers in patients with RA	• Exploratory endpoints The following exploratory disease activity parameters for RA will be assessed: ○ American College of Rheumatology (ACR) 20/50/70 response criteria ○ Disease activity score 28 (DAS28) ○ Clinical disease activity index (CDAI) ○ Simplified disease activity index (SDAI) The following exploratory biomarkers will be assessed: ○ Matrix metalloproteinase-3 (MMP-3) ○ Granulocyte macrophage colony-stimulating factor (GM-CSF) ○ C-X-C motif chemokine ligand 10 (CXCL10) ○ C-C motif chemokine ligand 2 (CCL2) ○ Cartilage oligomeric matrix protein (COMP) ○ Tumor necrosis factor (TNF)-alpha ○ TNF-R1 ○ Interleukin-6 (IL-6)

4 Study Design

4.1 Overall Design

This is a Phase 1, multi-center, double-blind, randomized, placebo-controlled, MAD study to evaluate the safety, tolerability, and PK of orally administered TCK-276 in both males and females with RA. Blood samples for possible future pharmacogenetic, possible future metabolite assessments, and possible future pharmacodynamic (PD) assessments will be collected.

A total of thirty-two (32) patients with RA will be enrolled in this clinical study. This MAD study will consist of 4 cohorts of 8 patients (6 active treatment and 2 matching placebo, or a 3:1 ratio), each receiving an oral dose of TCK-276 or matching placebo for 7 days (QD under fed condition) as shown in Figure 1–1. The first cohort will be divided into 2 subgroups to implement the sentinel dosing approach. Within the cohort, the first subgroup will consist of 2 sentinel patients; one patient will receive TCK-276, and one patient will receive matching placebo. The second subgroup will consist of 6 patients (5 active treatment, 1 matching placebo). Individual patients in the second subgroup will be dosed at least 72 hours after the first dose of the second patient of the first subgroup following a decision by the Investigators based on all available safety data from the sentinel patients up to 48 hours post-dose. Subsequent cohorts (cohort 2-4) will not include the sentinel dosing approach.

Patients will be admitted to the site from the morning of Day -1 and sequestered for the duration of the treatment (dosing) period. Each patient will receive QD oral doses of either TCK-276 or matching placebo administered as tablets under fed condition in the morning of Day 1 to Day 7. The patients will be discharged on Day 10. The planned dose levels to be tested are 10 mg (Cohort 1), 25 mg (Cohort 2), 75 mg (Cohort 3), and 150 mg (Cohort 4) of TCK-276. Based on the results from the SAD study (5 mg to 185 mg dosing) and the projected clinical effective dose (i.e., 75 mg), 10 mg is selected as the starting dose level in the MAD study. The dose in Cohorts 2, 3, and 4 may be adjusted based on the safety and PK results from the previous cohorts, if necessary. The overall exposure to TCK-276 (in terms of geometric mean area under the plasma concentration-time curve over a dosing interval [AUC_{tau}, tau = 24 hours]) on Day 7 would not be expected to exceed [redacted]. Further details are presented in Figure 4–1.

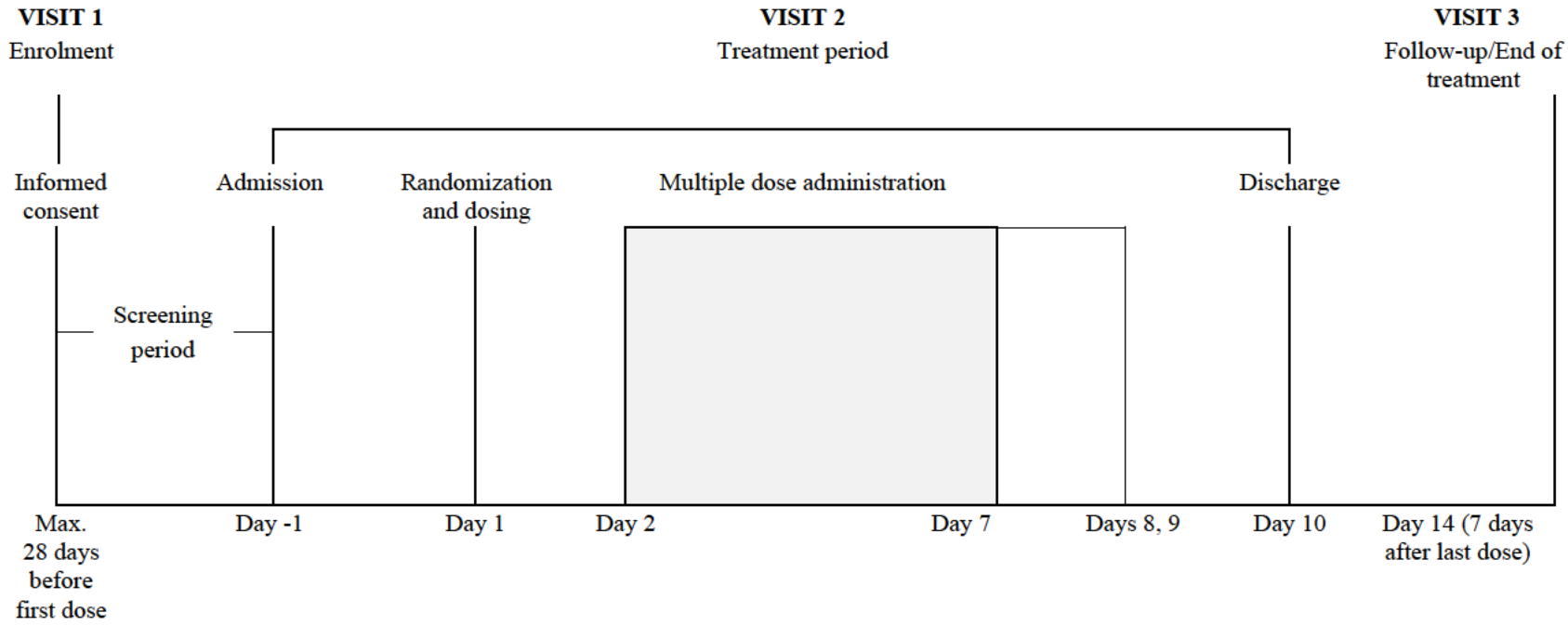
Dose escalation will only be allowed after blinded assessment of all safety, tolerability, and PK data up to Day 10 from each previous cohort evaluated by Investigators, Medical Monitor, and Sponsor representatives during the Safety Review Committee (SRC) meeting.

All patients (including patients who terminate the study early) will return to the site 13 days after the first TCK-276 or TCK-276 matching placebo administration for follow-up procedures and for the end of treatment examination.

Duration of patient participation from the Screening Visit to the end of treatment examination will be approximately 42 days. This includes 27 days for the Screening period, 11 days for the in-house Treatment period (patients will be confined from the morning of Day -1 until all safety assessments have been completed on Day 10), and 4 days after the end of the Treatment period, for the Follow-up/EOT Visit.

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, the clinical study may be terminated after appropriate consultation between the involved parties. The clinical study may also be terminated at the Sponsor's discretion in the absence of such a finding.

Figure 4–1 Study Flow Chart – Multiple Ascending Dose Design



4.2 Scientific Rationale for Study Design

This study evaluates the safety, tolerability, and PK of ascending multiple doses of TCK-276 administered as oral tablet(s). The design is standard and is considered appropriate to meet the objectives of this exploratory study.

A double-blind, placebo-controlled study is appropriate and standard for an ascending multiple dose study. This design will minimize bias and provide reference data (i.e., data from placebo-treated patients) which will aid in the interpretation of results. The SRC will review available blinded safety, tolerability, and PK data after each cohort to confirm whether it is safe to proceed with the next planned dose, whether the dose escalation should be stopped, or if the dose should be lowered, repeated or titrated in the subsequent cohort.

The safety assessments for the study are accepted measures for ensuring safety of patients during a clinical study. The PK sampling schedule is considered appropriate given the information available. The justification for dose selection is discussed in Section 4.3.

4.3 Justification for Dose

In the SAD study, which included dose-levels up to 185 mg (capsule), TCK-276 was generally safe and well tolerated in healthy subjects with no reports of SAEs nor discontinuations due to AEs. The starting dose for the MAD study (10 mg, tablet) is sufficiently lower than the highest dose in the SAD study (185 mg, capsule), and the projected clinical effective dose (75 mg) that was calculated from nonclinical pharmacological study using the rat adjuvant-induced arthritis model.

Patients with RA will be enrolled in this MAD study. Given the data for recently approved RA drugs, an up to 2-fold increased exposure in patients with RA compared to healthy subjects was taken into consideration as a conservative approach. Even if a 2-fold higher exposure in patients with RA would occur, the exposure of the 10 mg in the MAD study corresponds to 20 mg in healthy subjects, which is sufficiently lower than that of the highest dose in the SAD study (185 mg) and the projected clinical effective dose (75 mg).

Therefore, 10 mg as tablet formulation is considered the appropriate starting dose in the MAD study.

The dosing frequency (i.e., QD) was selected considering the PK characteristics of TCK-276 and patient's convenience. The dosing duration (7 days) was considered sufficient to achieve steady state conditions.

Dose Escalation

In this MAD study, the dose escalation progression will be from 10, 25, 75, and up to 150 mg in subsequent cohorts. The overall exposure to TCK-276 (in terms of geometric mean AUC_{tau}) on Day 7 is not expected to exceed the predefined AUC cap [redacted]. The exposure at 150 mg dosing in tablet formulation is assumed to be less than the predefined AUC cap based on the results from the SAD study (5 mg to 185 mg, capsule). Therefore, 150 mg is chosen for the highest dose. The dose in Cohorts 2, 3, and 4 may be adjusted based on the safety and PK results from the previous cohorts, if necessary. Dose escalation will only be allowed after blinded assessment of all safety, tolerability, and available PK data up to Day 10 from each previous cohort evaluated by Investigators, Medical Monitor, and Sponsor representatives during the SRC meeting.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the Schedule of Activities (SoA) (Table 1-1).

A patient is considered to have completed the study if he/she has completed all periods of the study including the last visit.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The study population will consist of patients with RA. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in the clinical study:

1. Patient voluntarily agrees to participate in this study and signs an Institutional Review Board (IRB) approved informed consent prior to performing any of the Screening Visit procedures.
2. Patient is able to understand and is willing to comply with all study requirements, and willing to follow the instructions of the study staff.

3. Diagnosis of RA and meeting the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA[9](total score 6 or greater/10 diagnosed at least 3 months prior to the Screening Visit).
4. Patient between the ages of 18 and 64 years, inclusive, at the Screening Visit.
5. Female patient must be not pregnant, not breast feeding and one of the following conditions need to apply:

    a. Of non-childbearing potential based on documented surgical treatment (hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal, meaning patient had spontaneous amenorrhea for at least 12 months without alternate medical cause prior to Screening Visit and follicle stimulating hormone (FSH) > 40 U/mL at the Screening Visit.

OR

    b. Of childbearing potential and using a highly effective method of contraception (failure rate of < 1% per year) and agrees to remain on a highly effective method from the time of signing the informed consent form (ICF) until 21 days after the last dose.

6. Male patient must agree to stay abstinent or must use together with his female partner(s) a form of highly effective contraceptive (failure rate of < 1% per year) from the time of signing the ICF until up to 3 months after the last dose of the study drug.
7. Nonsmokers (or other nicotine use) as determined by history (no nicotine use over the past one year prior to the Screening Visit) and by negative urine cotinine concentration (< 200 ng/mL) at the Screening Visit and at Admission.
8. Body mass index (BMI) between 18.5 and 32.0 kg/m^2, inclusive, at the Screening Visit.
9. Patient is required to have completed a COVID-19 vaccine regimen within no more than 5 months prior to screening to be eligible for the study.
10. Permitted concomitant medications for any reason, must be on a stable dose (12 weeks for methotrexate and anti-malarials and at least 30 days for other medications prior to the Screening Visit).

    Permitted medications include: anti-malarials; nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors at approved dosage, and low dose oral corticosteroids (prednisone ≤ 10 mg/day or equivalent); methotrexate ≤ 25 mg by mouth (PO) or subcutaneous (SC) weekly concomitantly with folic acid or folinic acid.

5.2 Exclusion Criteria

Patients who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Female patients who are breastfeeding or have a positive urine pregnancy test either at the Screening Visit or at Admission.
2. Patients who are unable to eat the prescribed meals during the stay at the site; vegetarian or vegan.
3. Patient has a history of significant drug allergy, as determined by the Investigator.
4. Patient has used a study drug, any prohibited medication(s) (see Section 6.8.2), over-the-counter (OTC) medications, vitamins, dietary and herbal supplements within 14 days or 5 half-lives if known (whichever is longer) prior to the first dose of study drug.
5. Patient has a history of active suicidal ideation in the past 6 months prior to the Screening Visit, or any psychiatric disorders that will affect the patient's ability to participate in the study as determined by the Investigator.
6. Patient has a current or recent (within 14 days prior to the Screening Visit) history of uncontrolled, clinically significant infectious, hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease.
7. Patient with any of the following laboratory abnormalities either at the Screening Visit or at Admission. These assessments may be repeated once at the discretion of the Investigator.
    a. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal (ULN)
    b. Bilirubin ≥ 1.5 times ULN
    c. An estimated glomerular filtration rate (eGFR) according to Cockcroft-Gault ≤ 60 mL/min
    d. Hematology values below the lower limit of normal: Neutropenia, absolute neutrophil count < 1000/mm^3, hemoglobin < 9 g/dL, white blood cell < 2.5 × 10^3/μL
    e. Clinically significant abnormalities, as judged by the Investigator
8. Patient has a history of alcohol and/or drug abuse within 24 weeks of the Screening Visit.
9. Patient has positive results for drug testing either at the Screening Visit or at Admission.
10. Patient has positive breath alcohol test either at the Screening Visit or at Admission.

11. Regular consumption of alcohol within 6 months prior to the Screening Visit (> 7 drinks/week for females, > 14 drinks/week for males where 1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor), or use of drugs of abuse (such as marijuana) within 3 months prior to the Screening Visit.
12. Patient has positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis B core (HBc) antibodies, hepatitis C virus (HCV) antibody, and/or human immunodeficiency virus (HIV) antibody at Screening Visit.
13. Patient has QT interval corrected for heart rate (QTc) using Fridericia's correction (QTcF) > 450 ms for males or QTcF > 470 ms for females either at the Screening Visit or Admission, based on safety 12-lead electrocardiogram (ECG). Patient has Screening or Admission ECG with second- or third-degree atrioventricular block, bundle branch block, arrhythmia (but not sinus arrhythmia or supraventricular premature beats), or illegible QT interval.
14. Patient has history or evidence of cardiopathy, acute coronary syndrome, hypertrophic cardiomyopathy, myocarditis or QT prolongation syndrome.
15. Patient is unwilling to abstain from drinks and foods containing alcohol, grapefruit, or caffeine (including coffee, tea, coke, energy drinks, or chocolate) starting 72 hours prior to the Admission until Day 14 Follow-up Visit.
16. Patient has donated blood or experienced acute blood loss (including plasmapheresis) of greater than 500 mL within 90 days prior to the first dose of study drug.
17. Patients with a known immunodeficiency disorder. Have a history of a major organ transplant or hematopoietic stem cell/marrow transplant.
18. Patients with infections requiring treatment or hospitalization within 14 days prior to the Screening Visit, parenteral antimicrobial therapy within 60 days prior to the Screening Visit, infected joint prosthesis; history of herpes zoster, active herpes simplex, or herpes simplex on suppressive therapy.
19. Patient has a chronic hepatic disease or hepatic impairment.
20. Patient has a history of *Mycobacterium tuberculosis* or positive interferon gamma release assay for tuberculosis (IGRA-TB) or abnormal chest X-ray (for positive IGRA-TB patients) at the Screening Visit.
21. Patient has a history of any lymphoproliferative disorder.
22. Patient has a history of COVID-19 unless fully recovered with no sequalae for 14 days.
23. Patient who had a severe course of COVID-19 (extracorporeal membrane oxygenation, mechanically ventilated).

24. Patient who has recent (within 14 days prior to the Screening Visit or between the Screening Visit and Admission) exposure to someone who has COVID-19 symptoms or positive test result.
25. Patient who has a positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 either at the Screening Visit or at Admission.
26. Patient who has clinical signs and symptoms consistent with SARS-CoV-2 infection; e.g., fever, dry cough, dyspnea, sore throat, fatigue, or positive SARS-CoV-2 test result within 14 days prior to and including either the Screening Visit or Admission.
27. Patients may not receive any live/attenuated vaccine from 30 days prior to the Screening Visit until Day 14 Follow-up Visit.
28. COVID-19 vaccine should not be given 1 week prior to the Screening Visit.
29. Patients treated with any other medications listed under Inclusion Criteria #9 including all medications listed in Section 6.8.2.
30. Patients with malignancy or history of malignancy except adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ. Previous treatment with total lymphoid irradiation.
31. History of recurrent inflammatory joint disease other than RA (e.g., gout, Lyme disease) or history of any other autoimmune rheumatic diseases other than Sjogren's syndrome.
32. Major surgery within 30 days prior to the Screening Visit or patients with planned surgery.
33. Patients who have an abnormal chest X-ray for interstitial lung disease (ILD) at the Screening Visit and/or patients with history of ILD.
34. History of fainting or family history of sudden death.
35. Patient has any disorder that would interfere with the absorption, distribution, metabolism or excretion of study drug.
36. Patient has a history of deep vein thrombosis and/or pulmonary embolism.
37. Patient has poor venous access.
38. Patient is an employee of the clinical research team (any Teijin or research site employee) or has a family member who is an employee of these organizations.

39. Patient is unable to understand the protocol requirements, instructions, study related restrictions, nature, scope, and possible consequences of the clinical study. Patient is unlikely to comply with the protocol requirements, instructions and study related restrictions; e.g., uncooperative attitude, inability to return for Follow-up Visits and improbability of completing the clinical study.
40. Patient is judged as inappropriate for study participation by the Investigator for other reasons.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Refrain from consumption of grapefruit foods or beverages, or Seville-orange containing foods (e.g., orange marmalade) or beverages from 72 hours before Admission until Day 14.

5.3.2 Caffeine, Alcohol, and Tobacco

1. During each dosing session, patient will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 72 hours before Admission until Day 14.
2. During each dosing session, patients will abstain from alcohol and alcohol-containing foods, medications, or beverages for 72 hours before Admission until Day 14.
3. Patients who use tobacco products will be instructed that use of nicotine-containing products (snuff, chewing tobacco, cigars, pipes, vaping tobacco products or nicotine-replacement products such as nicotine chewing gum and nicotine plasters) will not be permitted from 1 year before the Screening Visit until Day 14.

5.4 Screen Failures

A screen failure occurs when a patient who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (e.g., eligibility requirements failed), and documentation of any medical occurrences that qualify as SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened patients should be assigned a new patient number for every Screening/Rescreening event.

5.4.1 Screening and Enrollment Log and Patient Identification Numbers

The patient's enrollment will be recorded in the Screening and Enrollment Log.

Upon enrollment, each patient will receive a unique patient identification number. Patient numbers must not be re-used for different patients.

6 Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1 Study Intervention(s) Administered

Study drug and study cohorts are summarized in Table 6–1 and Table 6–2, respectively.

Table 6–1 Study Intervention(s) Administered

Intervention Label	TCK-276	Placebo for TCK-276
Intervention Name	TCK-276	Placebo
Intervention Description	TCK-276 or matching placebo is orally administered QD under fed condition in the morning of Day 1 to Day 7.	
Type	Drug	
Dosage Formulation	Tablet	
Unit Dose Strength(s)	10 mg or 25 mg	NA
Dosage Level(s)	10 mg (Cohort 1), 25 mg (Cohort 2), 75 mg (Cohort 3), and 150 mg (Cohort 4) of TCK-276 QD	Matching placebo QD
Route of Administration	Oral	
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	
Sourcing	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.	
Packaging and Labeling	Study drug will be packaged and labeled in accordance with applicable local and regulatory requirements.	The matching placebo will be packaged and labeled in accordance with applicable local and regulatory requirements.

AxMP = auxiliary medicinal product; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; QD = once daily.

Table 6–2 Study Cohorts

Cohort Title	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Cohort Type	Experimental			
Cohort Description[1]	Patients will receive TCK-276 10 mg QD under fed condition in the morning of Day 1 to Day 7.	Patients will receive TCK-276 25 mg QD under fed condition in the morning of Day 1 to Day 7.	Patients will receive TCK-276 75 mg QD under fed condition in the morning of Day 1 to Day 7.	Patients will receive TCK-276 150 mg QD under fed condition in the morning of Day 1 to Day 7.
Associated Intervention Labels	Investigational drug			

QD = once daily.

1. The first cohort will be divided into 2 subgroups that will consist of 2 sentinel patients (1 active treatment, 1 matching placebo) and 6 patients (5 active treatment, 1 matching placebo) to implement the sentinel dosing approach.

6.2 Preparation, Handling, Storage, and Accountability

TCK-276 tablets are packaged in high density polyethylene (HDPE) bottles containing a desiccant and polyethylene (PE) pharmaceutical coil with polypropylene (PP) caps (30 tablets/bottle). Placebo is provided for to match size, color, and weight of TCK-276 tablets (10 mg or 25 mg).

The Investigator or designee must maintain a log to confirm appropriate temperature conditions (20°C to 25°C [68°F to 77°F]) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only patients enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability and record maintenance (e.g., receipt and final disposition records).

Following completion of the clinical phase of the study and Sponsor review of accountability, all unused supplies will either be returned to the Sponsor (together with the accountability records)

or will be destroyed locally in agreement with the Sponsor and Certificates of Destruction provided to the Sponsor.

Further guidance and information for the final disposition of unused study intervention are provided in the study reference manual or other specified location.

6.3 Measures to Minimize Bias: Randomization and Blinding

Table 6–3 Measures to Minimize Bias

Study using IRT	All patients will be centrally randomized using an IRT. Each patient will be assigned a unique number (randomization number) that encodes the patient's assignment to a treatment group within one of the 4 cohorts of the study, according to the randomization schedule generated by IRT using a validated computer program. Details of the procedure are described in the IRT Manual provided to all sites. Study intervention will be administered/dispensed at the study visits as summarized in the SoA (Table 1-1). Returned study intervention should not be re-dispensed to the patients.
Blind break (IRT)	This is a double-blind study in which patients/care providers/Investigators/outcomes assessors, are blinded to study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's study intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a patient's study intervention assignment unless this could delay emergency treatment for the patient. If a patient's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

Blinded study with unblinded third party who is dispensing intervention	Patients will be randomly assigned in a 3:1 ratio to receive study intervention. Investigators will remain blinded to each patient's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. This third party will instruct the patient/patient's LAR to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the Investigator. In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.

IRT = Interactive Response Technology; LAR = legally authorized representative.

Sponsor safety staff may unblind the intervention assignment for any patient with an SAE. If the suspected unexpected serious adverse reaction (SUSAR) requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.4 Study Intervention Compliance

When patients are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Dose Modification

The dosing schedule may be adjusted based on the safety and PK results, if necessary, to expand a dosing cohort to further evaluate safety, and/or PK findings at a given dose level or to add cohorts to evaluate additional dose levels. The study procedures for these additional patient(s)/cohort(s) will be the same as that described for other study patients/cohorts.

6.6 Continued Access to Study Intervention After the End of the Study

Study intervention for RA will not continue beyond this study.

6.7 Treatment of Overdose

For this study, any dose of TCK-276 greater than 10 mg (Cohort 1), 25 mg (Cohort 2), 75 mg (Cohort 3), and 150 mg (Cohort 4) within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

a. Contact the Medical Monitor immediately.
b. Evaluate the patient to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
c. Closely monitor the patient for any AE/SAE and laboratory abnormalities until TCK-276 can no longer be detected systemically.
d. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
e. Document the quantity of the excess dose as well as the duration of the overdose.

6.8 Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

a. reason for use
b. dates of administration including start and end dates
c. dosage information including dose and frequency

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

6.8.1 Permitted Medications

Permitted medication includes anti-malarials nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors at approved dosage, low dose oral corticosteroids (prednisone ≤ 10 mg/day or equivalent); methotrexate ≤ 25 mg PO or SC weekly concomitantly with folic acid or folinic acid.

6.8.2 Prohibited Medications

Prohibited medications may include, but are not limited to, those listed in Appendix 6 (Section 10.6). These listings of prohibited concomitant treatments are not considered all inclusive. If the use of these types of medications is medically necessary during the course of the study, the Investigator must contact the Sponsor Medical Monitor to discuss further administration of TCK-276. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

6.8.2.1 Caution

[redacted] Investigators should recognize potential interactions with these drugs and avoid maximum doses, if possible, if these drugs are used. Cautioned medications may include, but are not limited to, those listed in Appendix 6 (Section 10.6). These listings of cautioned concomitant treatments are not considered all inclusive.

7 Discontinuation of Study Intervention and Patient Discontinuation

7.1 Discontinuation of Study Intervention

It may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the patient will remain in the study to be evaluated for clinical observation and safety monitoring. See the SoA (Table 1-1) for data to be collected at the

time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Overall Study Stopping Criteria

The study will be stopped if any of the following occur and are thought to be at least possibly related to study intervention agreed upon by the SRC:

- Two patients develop the same Grade 3 AE (grading is based on the Common Terminology Criteria for Adverse Events [CTCAE] version 5.0).
- One patient develops ≥ Grade 4 AE (CTCAE version 5.0).
- Death of a patient at any time.

If any of the following scenarios occur within a cohort with reasonable possibility of a causal relationship with study drug, dosing will be stopped, and further dosing will not be initiated.

- One or more patients experience increased alanine ALT or AST > 3 × ULN with total bilirubin (TBL) > 2 × ULN or increased AST > 3 × ULN accompanied by alkaline phosphatase (ALP) > 1.5 × ULN.
- One or more patients experience a decrease of absolute neutrophil count less than 1,000/mm^3 or white blood cell (WBC) less than 2.5 × 10^3/μL or platelet count less than 75,000/μL.
- One or more patients have an increase of more than 60 ms in QTcF compared to the baseline QTcF (baseline QTcF = value obtained on Day 1 at pre-dose in the treatment period) or QTcF > 500 ms or other clinically significant conduction disturbance or arrhythmia. All ECGs for this determination must be performed under strict resting conditions.
- Two or more patients, who receive study intervention, have tachycardia defined as resting supine heart rate > 125 beats per minute (bpm) persisting for at least 10 minutes.
- Two or more patients, who receive study intervention, have symptomatic bradycardia defined as resting supine heart rate < 40 bpm accompanied with symptoms of bradycardia while awake persisting for at least 10 minutes.
- Two or more patients, who receive study intervention, develop hypertension defined as an increase in resting supine systolic blood pressure (BP) > 40 mmHg to above a reading of 180 mmHg and persisting for at least 10 minutes.

If the criteria were met, the SRC will carefully review the totality of data, considering moderate non-serious AEs at least possibly related to the study intervention administration in unblinded

fashion, the number of patients in which they occur, concurrency of more than one within the same patient. Although changes from normal ranges are most relevant, changes from baseline measurements will also considered observing any trends. If consensus among the voting SRC members cannot be reached, then the Principal Investigator, who has the ultimate responsibility for the safety of the patients, will make the final decision.

7.1.2 Dose Escalation

After each sub-cohort and cohort, the Principal Investigator and the SRC will evaluate the safety, tolerability data and available PK data up to Day 10 to determine the next dose. The predefined AUC_{tau} [redacted] level will be used in the SRC as a benchmark so that the human exposure can be compared with preclinical exposure data. The safety and PK data from all patients in the previous cohort must be reviewed before a decision to escalate the dose can be made. Dose escalation will only occur if data from a minimum of 6 patients have been reviewed from the previous lower dose group, such that data from a minimum of 4 patients who have received active treatment will be used to make the dose escalation decision (based on the randomization of 6 active treatment:2 matching placebo).

Doses will not exceed a dose level at which the geometric mean of AUC_{tau} exceeds or would be anticipated to exceed the following limits:

[redacted]

If PK data indicate that the predefined AUC [redacted] has been achieved or would be exceeded with escalation to the next higher dose, dose escalation will be stopped. A dose in which the stopping criteria have been met will not be repeated and further dose escalation will not occur. Where stopping criteria have not been met, the decision of the SRC may be to give the next intended dose, a smaller than the predefined dose increment, a repeated dose or to stop dosing. The SRC will make the decision for the next dose level (to give the next intended dose, a greater or smaller dose increment than the intended dose, a repeated dose) or whether to stop the study after reviewing all the pertinent safety and any other relevant data and decision of the voting members. If consensus among the voting SRC members cannot be reached then the Principal Investigators, who have the ultimate responsibility for the safety of the patients, will make the final decision on the next dose level or whether to stop the study. In any event, dose escalation can only occur if agreed by the Principal Investigators. The decisions of the SRC on the next dose level will be documented and provided to all the appropriate parties

involved with the study, including the pharmacist to enable study intervention preparation for the next scheduled dosing day.

Initially the data will be reviewed blinded, but if the Principal Investigators or the SRC consider it necessary due to a safety concern, either individual patients or the entire cohort may be unblinded to enable decision making. Before breaking the code, the potential decisions and actions should be determined. The code will be broken according to local standard operating procedures (SOPs). Following review of data from a cohort of patients, the timing of assessments and/or blood samples may be adjusted for subsequent cohorts.

Dose escalation will be stopped if any of the following occur and are thought to be at least possibly related to study intervention agreed upon by the SRC. It is determined that the limit of safety and/or tolerability has been reached as determined by the SRC.

- Two or more of the patients in a cohort develop ≥ Grade 2 AEs (CTCAE version 5.0) in the same category, related to TCK-276, as judged by the Investigator.
- One or more patients in a cohort develop ≥ Grade 3 AEs (CTCAE version 5.0) in the same category, related to TCK-276, as judged by the Investigator.

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. The patient will be permanently discontinued from the study intervention and the study at that time.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1-1). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

In addition to the stopping rules described in Section 7.1.1, a patient will be withdrawn by the Investigator or designee from the study and not be allowed to continue with the study if any of the following criteria are fulfilled:

- Any patient who develops an AE ≥ Grade 3 (CTCAE version 5.0).

- Patient will be discontinued from further dosing if following toxicities are observed:
    - Hematologic: Neutropenia, absolute neutrophil count < 1000/mm^3, hemoglobin < 9 g/dL, white blood cell < 2.5 × 10^3/μL
    - Renal: serum creatinine > 3 × ULN
    - Hepatic: bilirubin elevation > 2 × ULN; AST or ALT elevation > 3.0 × ULN
    - QTcF prolongation: mean QTcF ≥ 500 ms or change from the nearest baseline > 60 ms
    - ECG abnormalities including ventricular tachycardia or ventricular fibrillation, complete heart block (Grade III atrioventricular block) or second degree atrioventricular block Mobitz type II
    - Hypertension: resting systolic BP ≥ 180 mmHg and ≤ 80 mmHg diastolic BP
      Hypotension: resting systolic BP ≥ 110 mmHg and ≤ 40 mmHg diastolic BP
    - Pulse (resting) < 35 or > 110 bpm
- A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or administrative reasons.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn patients may be replaced if patient withdrawal is not due to safety or tolerability reasons.
- Refer to the SoA for assessments to be performed at the time of study discontinuation.
    - At the discretion of the Investigator or designee, the patient may continue with study assessments after discontinuation until the final Follow-up Visit procedures are performed. A reasonable effort will be made to determine the reasons why a patient fails to return for the necessary visits or is discontinued from the study. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the study center.

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. All patients who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a patient withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge.

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event
2. Protocol violation
3. Loss to follow-up
4. Patient withdrew consent at own request
5. Other

A genuine effort must be made to determine the reasons why a patient fails to return for the necessary visits or is discontinued from the study. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the clinic.

Patients who are withdrawn after randomization for non-drug-related reasons may be replaced following discussion between the Investigator and the Sponsor. Patients withdrawn after randomization as a result of AEs thought to be related to the study drug will generally not be replaced.

7.3 Lost to Follow-Up

A patient will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

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

a. The site must attempt to contact the patient and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether the patient wishes to and/or should continue in the study.

b. In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record/case report form (CRF).

c. Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

d. Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Table 1-1). Protocol waivers or exemptions are not allowed.

A Safety Management Plan (SMP) will be signed between the Sponsor and [redacted].

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 600 mL

Blood samples of approximately 520 mL will be collected for measurement of blood concentrations of TCK-276 and TEI-W00595 as specified in the SoA (Table 1-1) throughout the study period. A maximum of 30 samples may be collected at additional timepoints during the

study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative Procedures

8.1.1 Informed Consent

Informed consent must be documented according to Appendix 1 (Section 10.1.3).

8.1.2 Patient Identification Card

All patients will be given a patient identification card identifying them as patients in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the patient with a patient identification card immediately after the patient provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the patient identification card.

8.1.3 Calibration of Equipment

The Investigator (or qualified designee) is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study that provides information about eligibility criteria and/or safety or efficacy parameters is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Screening and Eligibility Assessments

8.2.1 Eligibility Criteria

All inclusion and exclusion criteria (Section 5.1 and Section 5.2) will be reviewed by the Investigator or designee to ensure that the patient qualifies for the study. Recheck of clinical status will need to be performed before the first dose of study intervention.

8.2.2 Demography and Other Baseline Information

The following demographic information will be recorded:

- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height, without shoes (cm)
- Body weight, without shoes (kg)
- Body mass index (BMI) (kg/m^2)

Other baseline characteristics will be recorded as follows:

- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- Special diet (vegetarian and vegan)
- History of blood or plasma donation

8.2.3 Medical History

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 1 year that the Investigator considers to be clinically relevant. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

- The medical history comprises:
- General medical history
- Medication history
- Prior and concomitant medication
- Reproductive history
- Onset date of RA

- Criteria for the classification of RA used for the diagnosis
- History of surgery of RA
- Name of the RA treatment drugs used in the past

8.2.4 Prior and Concomitant Medications Review

The Investigator or qualified designee will review prior medication use and record prior medications taken by the patient.

The Investigator or qualified designee will record medication, if any, taken by the patient during the study through the last visit. Concomitant medications will be recorded until the last dose of study intervention (or longer if related to an SAE).

8.2.5 Screening Assessments

Patients who have signed an informed consent will undergo following procedures and assessments:

- Viral serology to HBsAg, anti-HBc antibodies, anti-HCV antibody, and/or anti-HIV types 1 and 2 antibodies
- Blood and urine drug screen to check the levels of amphetamines, barbiturates, benzodiazepines, oxycodone, tricyclic antidepressants, cannabinoids, cocaine, opiates, phencyclidine, 3,4-Methylenedioxymethamphetamine (MDMA) and propoxyphene
- Breath alcohol test by breathalyzer
- Interferon gamma release assay for tuberculosis (IGRA-TB) or abnormal chest X-ray
- Urine cotinine test
- SARS-CoV-2 test measured by real time RT-PCR
- Classification of disease stage/progression of RA
- For female patients, a urine β-human chorionic gonadotropin test must be used to confirm eligibility
- For female patients who are post-menopausal, FSH levels will be measured

Laboratory tests are listed in Table 10–1.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1-1).

8.3.1 Physical Examinations

Physical examinations will be performed at the time points detailed in the SoA (Table 1-1).

Full physical examination:

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

Brief physical examination:

An assessment of the general appearance, skin, cardiovascular system, respiratory system, and abdomen.

The brief physical examination may be extended to a full physical examination if considered necessary by the Investigators. Other evaluations may be performed as deemed necessary by the Investigators.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be assessed at the time points detailed in the SoA (Table 1-1). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Pulse (bpm)
- Body temperature (tympanic [ear] or non-contact infrared thermometers) (°C)
- Respiratory rate (breaths per minute)

Supine BP and pulse recordings will be made after the patient has been recumbent and at rest ≥ 5 minutes.

8.3.3 Electrocardiograms

Standard safety 12-lead ECGs will be performed at the time points detailed in the SoA (Table 1-1).

The12-lead ECGs will be performed after the patient has been resting supine for ≥ 5 minutes. The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval and QTc interval (QTcF).

All ECGs must be evaluated by a qualified physician for the presence of abnormalities.

8.3.4 Cardiac Telemetry

To allow a real-time assessment of cardiac safety at the study site, patients will be monitored by cardiac telemetry (for real-time assessment of cardiac rate and rhythm). Any clinically significant change noted on telemetry will be followed up with a 12-lead ECG. Further evaluation and treatment will be performed as deemed appropriate by the Investigators. Irrespective of the intervention, the ECG and continuous cardiac monitoring will be repeated hourly until the event resolves or the patient is deemed clinically stable by the Investigators.

8.3.5 Clinical Safety Laboratory Tests

Refer to Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Table 1-1) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically abnormal during participation in the study or within 2 months after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

a. If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.

b. All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Table 1-1).

c. If laboratory values from laboratory tests not specified in the protocol and performed at the institution's local laboratory result in the need for a change in patient management or are considered clinically relevant by the Investigator (e.g., are considered to be an SAE or an AE or require dose modification), then the results must be recorded.

8.3.6 Pregnancy Testing

Women of non-childbearing potential should only be included after a confirmed negative urine pregnancy tests at Screening and on Day - 1.

Women of childbearing potential should only be included after a confirmed negative urine pregnancy test at Screening, Days -1 and 14, and Early termination procedures.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The means of obtaining AE data should be described (volunteered, checklist, or questioning) as should any specific rating scales used and any specifically planned follow-up procedures for AEs or any planned re-challenge procedures.

Consider whether there any protocol-specific events that may need expedited reporting, or alternatively, are not required to be reported. Provide guidance for Investigators. If there is a specific AE that will be of special interest it should be described in Section 8.4.6.

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3).

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or a legally authorized representative [LAR]).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AE that are serious, considered related to the study intervention or the study, or that caused the patient to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Screening form including AE questioning will include specific questions regarding symptoms of COVID-19: fever, cough, dry throat, difficulty breathing, and potential exposure in the past 2 weeks.

Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded in the AE fields.

8.4.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All AEs and SAEs will be collected and recorded for each patient from the date for signing of ICF until Day 14 Follow-up Visit or early termination visit i.e., the patient has discontinued or completed Day 14 visit in the SoA (Table 1-1).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of awareness, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AESIs (as defined in Section 8.4), will be followed until resolution, stabilization, until the event is otherwise explained, or the patient is

lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.4.4 Regulatory Reporting Requirements for Serious Adverse Event

Prompt notification (within 24 hours, see Appendix 3 [Section 10.3]) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and forwarded to Investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female patients and, if indicated, partners of male patients will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 5.1.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female patients or partner of male patient (after obtaining the necessary signed informed consent from the partner) pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

The patient/pregnant partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient/pregnant partner and the neonate and the information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study patients/pregnant partners, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Prior to continuation of study intervention following pregnancy, the following must occur:

a. The Sponsor and the relevant IRB give written approval.
b. The patient gives signed informed consent.
c. The Investigator agrees to monitor the outcome of the pregnancy and the status of the patient and her offspring.

8.4.6 Adverse events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor to other parties might also be warranted.

AESIs are required to be reported by the Investigator to the Sponsor immediately (i.e., within 24 hours after learning of the event) regardless of their causality to the study treatment. The most appropriate diagnosis or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the eCRF and reported to the Sponsor immediately (i.e., within 24 hours after learning of the event), either as a SAE or an AESI. Based on CDK4/6 inhibition mechanism of action, the following AEs will be defined as AESIs:

- Myelosuppression: Hematology including monitoring for neutropenia, leucopoenia, thrombocytopenia, and increased tendency to bleed
- Embryo-fetal toxicity: highly effective methods of contraception will be used by the patients until 21 days after receiving the study drug
- Interstitial lung disease: Pulmonary symptoms (dyspnea, pyrexia, and cough)
- Gastrointestinal toxicity: e.g., diarrhea, nausea, vomiting, and abdominal pain

8.5 Pharmacokinetics

8.5.1 Blood Sample Collection

Blood samples will be used to evaluate the PK of TCK-276. Each plasma sample will be divided into 4 aliquots (1 each for the PK, the possible future metabolite assessments, a backup for the PK, and a backup for the possible future metabolite assessments). Samples collected for analyses of TCK-276 plasma concentration may also be used to evaluate safety or efficacy aspects that address concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples. Patient confidentiality will be maintained. At visits during which samples for the determination of plasma concentration of TCK-276 will be taken, 1 blood draw of sufficient volume can be used.

Intervention concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.2 Urine Sample Collection

Urine samples for the analysis of TCK-276 will be collected at the timepoints detailed in the SoA (Table 1-1). Urine will be collected at the following time intervals relative to study drug dosing: 0 to 6 hours, 6 to 12 hours, 12 to 24 hours after dosing on Day 1, and from 0 (pre-dose) to 6, 6 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after dosing on Day 7. Urine sample collection, processing and shipping details will be outlined in a separate laboratory manual. In brief, urine will be processed and analyzed by a validated method for concentrations of TCK-276. The PK parameters listed in Section 3 will be calculated from the urine concentration and volume of urine collected in each urine collection interval.

8.6 Exploratory Assessments

The following disease activity parameters will be evaluated in this study;

- ACR 20/50/70 1991 revised criteria for the classification of global functional status in RA on Days 1 and 7

- DAS28, CDAI, SDAI scores on Days 1 and 7

8.7 Genetics

A blood sample for DNA isolation will be collected from patients who have consented to participate in the optional pharmacogenomics component of the study. Patients who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement pharmacogenomic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample.

The final disposition of samples will be conducted per local regulations.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in a separate laboratory manual.

8.8 Biomarkers

Following biomarkers will be evaluated by the central laboratories in this study;

MMP-3, granulocyte macrophage colony-stimulating factor (GM-CSF), C-X-C motif chemokine ligand 10 (CXCL10), C-C motif chemokine ligand 2 (CCL2), cartilage oligomeric matrix protein (COMP), tumor necrosis factor (TNF)-α, TNF-RI, and interleukin (IL)-6 .

8.9 Health Economics

Health economics are not evaluated in this study.

9 Statistical Considerations

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the clinical study report (CSR).

9.1 Statistical Hypotheses

Not applicable.

9.2 Analysis Populations

For purposes of analysis, the following analysis populations are defined:

Table 9–1 Patient Analysis Population

Patient Analysis Population	Description
Randomized population	All patients that signed informed consent form and assigned randomization number.
Safety population	All randomized patients who received at least one dose of study drug (active/placebo).
PK population	All randomized patients with at least one quantifiable TCK-276 concentration.
Exploratory population	All randomized patients who received at least one dose of study drug (active/placebo) and have evaluable exploratory assessment data.

PK = Pharmacokinetics.

A summary table with the number of patients in each of the analysis population will be provided and this table will be displayed by cohort/treatment group and overall, for randomized population. A listing of patients excluded from analysis population will also be provided including reason of exclusion for randomized population.

9.3 Statistical Analyses

9.3.1 General Considerations

Continuous data will be summarized by cohort and treatment group using descriptive statistics (number, mean, standard deviation, minimum, median, and maximum). Categorical data will be summarized by cohort and treatment group using frequency tables (number and percentage).

9.3.1.1 Protocol Deviations

Protocol deviations will be listed by patient. Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately.

Protocol deviations will be handled in accordance with [redacted] SOPs.

9.3.1.2 Patient Disposition

Patient disposition will be summarized and will include the following information: number of patients randomized and dosed, number and percentage of patients completing the study and the number and percentage of patients who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on randomized population.

Patient discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

A randomization listing will be presented and include the following: each patient's randomization number, site, the treatment to which the patient has been randomized.

9.3.1.3 Demographic and Anthropometric Information and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight, and BMI) and disease activity data (ACR20/50/70, DAS28, CDAI, and SDAI) will be listed by patient. Demographic characteristics (age, sex, ethnicity, and race), anthropometric characteristics (height, weight, and BMI) and disease activity data (ACR20/50/70, DAS28, CDAI, and SDAI) will be summarized by cohort, treatment and for all patients in the safety analysis population.

Medical history data will be listed by patient including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing if applicable).

9.3.2 Primary Endpoint(s) Analysis

9.3.2.1 Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of study drug. Concomitant medications are those taken after first dosing (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by patient and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration, and indication.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) latest version.

9.3.2.2 Exposure

A listing of drug administration will be created and will include the date and time of administration.

9.3.2.3 Adverse Events

All AEs will be listed and coded according to the MedDRA. Adverse events will be individually listed per patient number, presenting assigned treatment, verbatim term, Primary SOC, PT,

treatment emergence (yes or no), date and time of onset, date and time of last study drug administration before AE, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, the required action taken, outcome, if it is a reason for drop out, and if it is AESI or not. The treatment emergent AEs will be summarized by MedDRA terms and treatment groups. It will include evaluation of the number of AEs and the number of patients reporting these AEs.

SAEs will be listed separately.

9.3.2.4 Clinical Laboratory Tests

A by-patient listing will be presented. Clinical laboratory tests (observed values and change from baseline) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters.

9.3.2.5 Vital Signs

A by-patient listing will be presented. Observed values as well as change from baseline data will be summarized descriptively in tabular format.

9.3.2.6 Standard 12-lead Electrocardiogram

Standard 12-lead ECG data (observed and change from baseline) will be listed for each patient and time point. Observed values and change from baseline will be summarized descriptively in tabular format. A categorical QTc analysis will also be performed.

9.3.2.7 Telemetry

Cardiac telemetry (real-time assessment) will assess the cardiac safety. A by-patient listing will be provided.

9.3.2.8 Physical Examination

Abnormal physical examination findings will be listed.

9.3.3 Secondary Endpoint(s) Analysis

9.3.3.1 Pharmacokinetics Analyses

Plasma concentrations of TCK-276 and TEI-W00595 will be listed and summarized by descriptive statistics and displayed graphically as appropriate.

Plasma PK parameters of TCK-276 and TEI-W00595 will be calculated using non-compartmental methods and tables, figures, and listings for PK parameters will be generated using PK population, as detailed in SAP.

Plasma metabolite (TEI-W00595) to parent (TCK-276) molar ratio based on C_{max} and AUC will be determined and summarized after first and last dose administration. Molar ratios will be calculated based on molecular weight of [redacted] for TCK-276 and [redacted] for TEI-W00595.

Urine PK parameters of TCK-276 will be listed and summarized as detailed in SAP.

Dose proportionality will be assessed using power model based on Days 1 and 7 C_{max} and AUC_{tau} values for TCK-276.

Further details of analysis of PK data will be provided in the SAP before database lock.

9.3.4 Other Analyses

Not Applicable.

9.3.4.1 Exploratory Analyses

Exploratory assessment data will be listed and summarized by descriptive statistics and displayed graphically as appropriate.

9.4 Sample Size Determination

Formal sample size calculations were not performed. Thirty-two patients were chosen based on feasibility and are considered sufficient to meet the study objectives of this exploratory study.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB of SAE or other significant safety findings as required by IRB procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations 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.

10.1.3 Informed Consent Process

The Investigator or their representative will explain the nature of the study, including the risks and benefits, to the patient or the patient's LAR and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or the patient's LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients 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 patient or the patient's LAR.

A patient who is rescreened is required to sign a new ICF as a new assigned patient number.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

10.1.4 Data Protection

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

The patient must be informed that their 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 patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5 Committees Structure

The SRC will consist of the following core members:

- Principal Investigators
- Medical Monitor
- Sponsor Medical Representative

The SRC may also request to have attendance of or off-line support and input from the following functions as required:

- Study and Sponsor Statisticians
- Sponsor and/or study Medical Specialists (e.g., Neurologist, ECG Center cardiologists, etc.)
- Study and Sponsor Pharmacokineticists

10.1.6 Dissemination of Clinical Study Data

A summary of the results of the clinical study together with a summary that is understandable to a layperson will be provided after the global end (or early termination) of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

10.1.7 Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of eCRFs will be provided in eCRF Completion Instructions.

The Investigator must permit study-related monitoring, audits, IRB review, and Regulatory Agency inspections and provide direct access to source data documents.

Monitoring details describing strategies, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 2 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.

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.8 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported 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.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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.

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is considered when the first site is activated and allowed to screen patients, which will be the study start date.

Study/Site Termination

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

The Investigator may initiate study site 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 site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator.
- Total number of patients included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.10 Publication Policy

The results of this study may be published or presented at scientific meetings after study completion. Before any data from this study are published on the initiative of the Investigator, the Investigator must obtain written approval from the Sponsor. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor at least 60 days prior to 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 site 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.

10.1.11 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/Competent Authority approval prior to implementation (if appropriate). In the USA: Following approval, the protocol amendment(s) will be submitted to the Investigational new drug (IND) under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11.1 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, and/or the Sponsor's Clinical QA Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor, and [redacted] if involved in monitoring/data management, of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by each local laboratory (for assessments of Screening and Day -1) and central laboratory (for assessments from Day 1 to last visit). Note that erythrocyte sedimentation rate (ESR) is not included in Table 10–1, and it will be assessed at local laboratory as part of disease activity data on Days 1 and 7, not as safety laboratory test.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 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.

Investigators must document their review of each laboratory safety report.

Table 10–1 Protocol-required Safety Laboratory Tests

Hematology	
White blood cell (WBC) count	Neutrophils (percentage and absolute count)
Red blood cell (RBC) count	Lymphocytes (percentage and absolute count)
Hemoglobin (Hb)	Monocytes (percentage and absolute count)
Hematocrit (HCT)	Eosinophils (percentage and absolute count)
Mean corpuscular volume (MCV)	Basophils (percentage and absolute count)
Mean corpuscular hemoglobin (MCH)	Platelet count
Mean corpuscular hemoglobin concentration (MCHC)	RBC distribution width
Reticulocytes (count and percentage)	
Coagulation	
Prothrombin time	International Normalized Ratio (INR)
Activated partial thromboplastin time (aPTT)	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Gamma glutamyl transferase (GGT)
Albumin	Glucose
Alkaline phosphatase (ALP)	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Phosphorus
Blood urea nitrogen (BUN)	Potassium

Calcium	Sodium
Chloride	Total bilirubin
Total cholesterol	Total protein
Creatinine	Triglycerides
Creatine kinase (CK)	C- reactive protein (CRP)
Follicle stimulating hormone (FSH) (Screening Visit only; Post-menopausal females only)	
Urinalysis	
Bilirubin	Blood
Glucose	pH and specific gravity
Ketones	Protein
Leukocytes	Urobilinogen
Nitrite	Color and appearance
Microscopic (only for abnormal urine stick test findings)-Hyaline casts, cellular casts, granular casts, RBC and WBC	Urinary creatinine (to exclude dilution effect)
Viral Serology	
Hepatitis B core antibody (anti-HBc)	Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies
Anti-hepatitis B surface antigen (HBsAg)	
Hepatitis C virus antibody (anti-HCV)	
COVID-19 Testing	
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription polymerase chain reaction (RT-PCR)	
Urine Drug Screening, Cotinine Test, and Alcohol Test	
Amphetamines	Cocaine
Barbiturates	Opiates
Benzodiazepines	Phencyclidine
Oxycodone	3,4-methylenedioxymethamphetamine (MDMA)
Tricyclic Antidepressants	Propoxyphene
Cannabinoids	Cotinine
Alcohol/Ethanol (to be tested using breathalyzer)	
Pregnancy Testing	
Urine human beta chorionic gonadotrophin	

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event

AE Definition
An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (e.g., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. Use one of the two example bullets regarding lack of efficacy depending on the type of study. For Phase 1 studies, neither of these examples will be included unless efficacy is an endpoint.
Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE=adverse event; ECG=electrocardiogram; SAE=serious adverse event.

10.3.2 Definition of Serious Adverse Event

An SAE is an AE that:
a. Results in death
b. Is life-threatening The term life-threatening in the definition of serious refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-up of Adverse Event, Serious Adverse Event, and Adverse Event of Special Interest

AE, SAE, and AESI Recording
When an AE/SAE/AESI occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE/AESI information. It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to Teijin America, Inc. in lieu of completion of the Teijin America, Inc. required form. There may be instances when copies of medical records for certain cases are requested by Teijin America, Inc. In this case, all patient identifiers, with the exception of the patient number, will be blinded on the copies of the medical records before submission to Teijin America, Inc. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.
Assessment of Severity
The Investigator will make an assessment of severity for each AE/SAE/AESI reported during the study and classify it into one of Grade 1 through 5 using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0: • 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 activities of daily living (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. *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as Grade 3 or higher.

Assessment of Causality
The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/AESI. The Investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in their assessment. For each AE/SAE/AESI, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AESI and has provided an assessment of causality. There may be situations in which an SAE/AESI has occurred, and the Investigator has minimal information to include in the initial report in the electronic data collection tool. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE/AESI data to the electronic data collection tool.** The Investigator may change their opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment. The following "binary" decision choice will be used by the Investigator to describe the initial causality assessment: Related: Reasonable possibility of a relatedness Not related: No reasonable possibility of relatedness. The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AE, SAE, and AESI
The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE, SAE, or AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the originally completed form. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of Serious Adverse Event and Adverse Event of Special Interest

SAE and AESI Reporting via Electronic Data Collection Tool
The primary mechanism for reporting an SAE/AESI will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE/AESI data collection tool (see next table) to report the event within 24 hours. The site will enter the SAE/AESI data into the electronic system as soon as it becomes available. When calling to report an SAE/AESI, state that you are reporting an SAE/AESI and give the Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title. The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE/AESI report and the Sponsor/[redacted] will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (Investigator Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE/AESI from a study patient or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE/AESI form (see next table) or by telephone. Contacts for SAE/AESI reporting can be found below.
SAE Reporting via Paper Data Collection Tool
Email or facsimile transmission of the SAE/AESI paper data collection tool is the preferred method to transmit this information. In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE/AESI paper data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE/AESI data collection tool within the designated reporting timeframes. Contacts for SAE/AESI reporting can be found below.
Suspected Unexpected Serious Adverse Reactions (SUSARs)
Any AE that is serious, associated with the use of the study intervention, and unexpected (SUSAR) has additional reporting requirements, as described below. If the SUSAR is fatal or life-threatening, associated with study intervention, and unexpected, regulatory authorities and IECs will be notified within seven calendar days after the Sponsor

learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study intervention, and unexpected, regulatory authorities and IECs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

AE=adverse event; IEC=Institutional Review Board; SAE=serious adverse event; SUSAR=suspected unexpected serious adverse reactions

Serious Adverse Events Contact Details

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

[redacted]

(See SAE Reporting Instructions)

[redacted]

1. Telephone the [redacted] to inform him/her that you are emailing/faxing a SAE form. If the [redacted] is not available or you are calling after business hours (8:30 am to 5:30 pm Eastern time, Monday to Friday), leave a message in their voice mailbox.
2. Provide the [redacted] with the Principal Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.
3. Email/Fax the SAE form and any supporting documentation to the [redacted] within 24 hours of becoming aware of the event.
4. After business hours, the [redacted] may be reached through [redacted] 24-hour answering service at [redacted]. Give the answering service the protocol number, the study intervention name, and the Sponsoring pharmaceutical company.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered to be a woman of childbearing potential:

1. Premenarchal
2. Premenopausal female with one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented tubal ligation
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

3. Post-menopausal female

- A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the post-menopausal range (> 40 U/mL) may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

10.4.2 Contraception Guidance

Male patients

Male patients with female partners of childbearing potential (including partners who are pregnant or breastfeeding [including pumping breast milk to feed to a child]) must use contraception if any of the following criteria are met:

- Genotoxic study medication
- Study medication where reproductive toxicology studies have not yet been conducted

- Study medication with demonstrated or suspected human teratogenicity/fetotoxicity at subtherapeutic exposure levels if relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame:

- 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.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- Agree to use a male condom when having penile-vaginal intercourse WOCBP who is currently pregnant.

In addition, male patients must refrain from donating sperm for the duration of the study and for 3 months after the final dose of study medication.

Male patients with a pregnant or breastfeeding (including pumping breast milk to feed to a child) partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the study and for at least 3 months after the final dose of study medication.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below. If the Investigator has another method not listed below but is proven to have a failure rate < 1%, then this method may be considered after discussion with the Medical Monitor or Sponsor study physician.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent

- Failure rate of < 1% per year when used consistently and correctly.
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - Oral

  - Intravaginal
  - Transdermal

- Progestogen only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable

Highly Effective Methods That Are User Independent

- Implantable progestogen only hormonal contraception associated with inhibition of ovulation:
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion

Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

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 medication. 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 patient.

- Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional urine pregnancy testing should be performed at monthly intervals during the treatment period and at End of Treatment/End of Study, after the final dose of study medication and as required locally.
- Pregnancy testing will be performed when pregnancy is suspected
- Pregnancy testing will be performed at Screening and at every post-Screening visit before study medication application.
- If a study patient is pregnant and stays in the study for observation no pregnancy testing will be performed as long as the pregnancy lasts.

10.4.2.1 Collection of Pregnancy Information

Male Patients with Female Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive the study drug. If the study patient is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will not be required after birth of the child or elective termination of pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. This applies only to female patients who receive the study drug. If the study patient is later found to be on placebo, then pregnancy data collection can stop. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect any follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required after birth of the child or elective termination of pregnancy. Any termination of the pregnancy will be reported, regardless of fetal state (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to study drugs by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue the study drugs and will be withdrawn from the study.

10.5 Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB allow, a blood sample will be collected for DNA analysis.

DNA samples will be used for research related to TCK-276 or RA and related diseases. They may also be used to develop tests/assays related to study intervention and/or interventions of this drug class and RA. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to TCK-276 (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to TCK-276 or study intervention of this class to understand the study disease or related conditions.

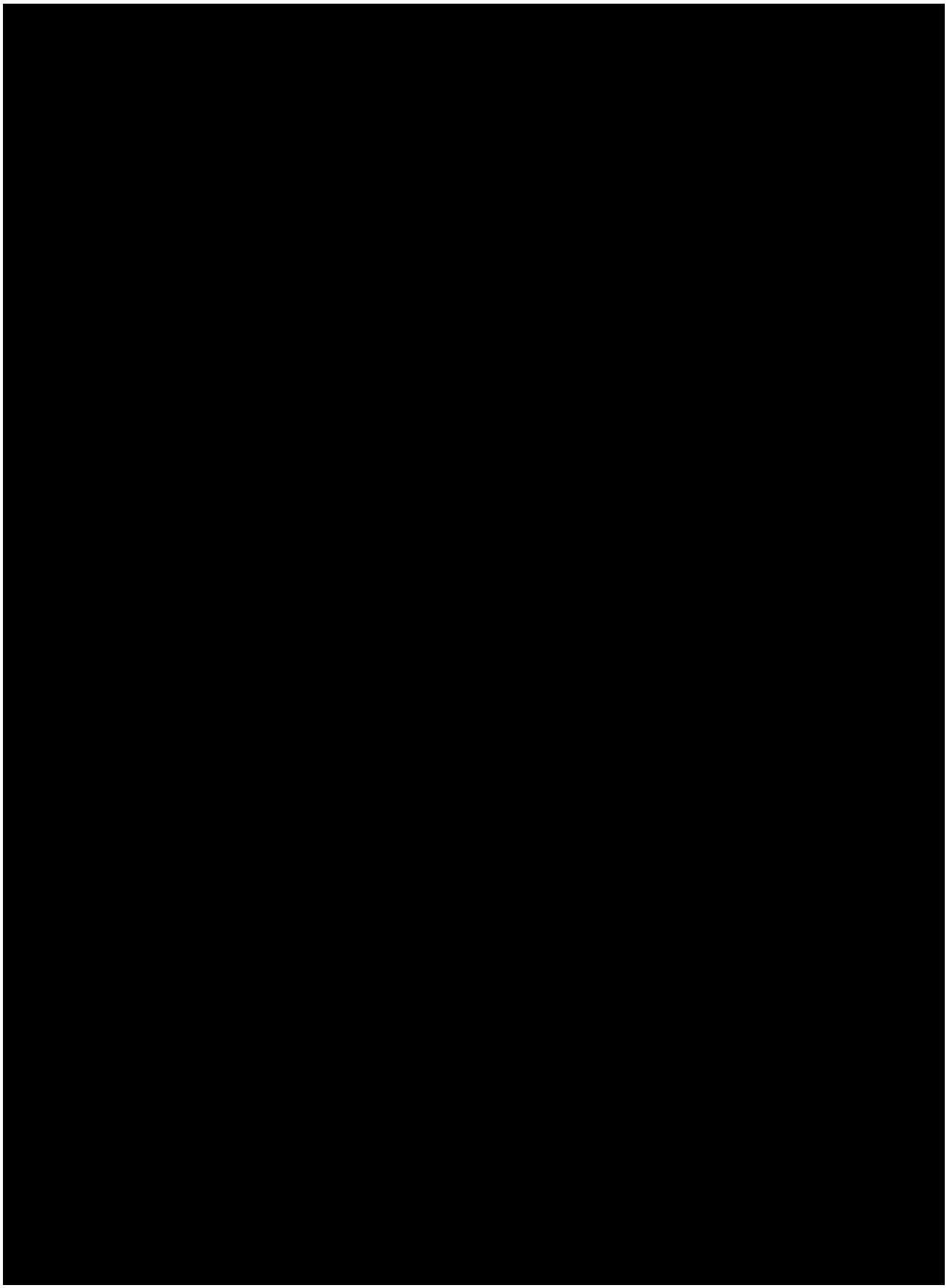
The results of genetic analyses may be reported in the CSR or in a separate study summary.

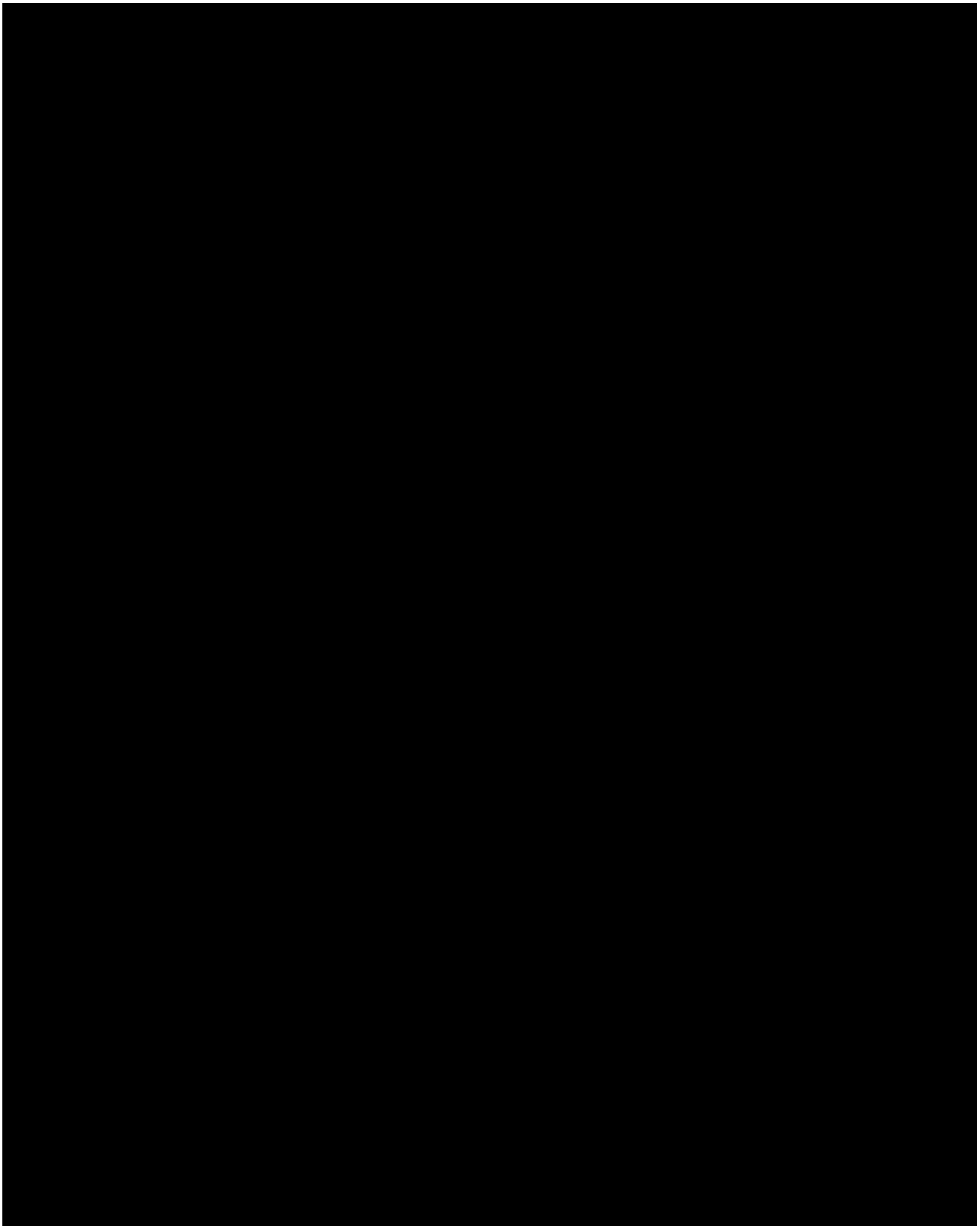
The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

10.6 [redacted]

Prohibited or cautioned medications may include, but are not limited to, those listed below. These listings of prohibited or cautioned concomitant treatments are not considered all inclusive.

[redacted]





10.7 Appendix 7: Abbreviations and Definitions

Abbreviations	Definition
ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse event of special interest
A_e	Amount of study drug excreted unchanged in the urine
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 pre-dose (time 0) extrapolated to infinite time ($AUC_{last} + C_{last}/\lambda z$) calculated using the linear-log trapezoidal rule
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve up to last measurable concentration
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve up to 24 hours
AUC_{tau}	Area under the plasma concentration-time curve over a dosing interval, tau = 24 hours
[redacted]	[redacted]
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CCL2	C-C motif chemokine ligand 2
CDAI	Clinical disease activity index
CDK	Cyclin dependent kinase
CFR	Code of Federal Regulations
CL/F	Apparent total body clearance
CL_r	Renal clearance
C_{max}	Maximum plasma concentration determined directly from the concentration-time profile
COMP	Cartilage oligomeric matrix protein
COVID-19	Coronavirus disease 2019
CRF	Case report forms
CRO	Contract research organization
CSR	Clinical study report

Abbreviations	Definition
CTCAE	Common Terminology Criteria for Adverse Event
CycD	D-type cyclins
[redacted]	[redacted]
CXCL10	C-X-C motif chemokine ligand 10
DAS28	Disease activity score 28
DDI	Drug-drug interaction
DMARD	Disease modifying antirheumatic drug
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FSH	Follicle stimulating hormone
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage colony stimulating factor
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IGRA-TB	Interferon gamma release assay for tuberculosis
ILD	Interstitial lung disease
IL-6	Interleukin-6
IMP	Investigational medicinal product
IRB	Institutional Review Board
LAR	Legally authorized representative
MAD	Multiple ascending dose
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMP-3	Matrix metalloproteinase-3
MR	Metabolic ratio

Abbreviations	Definition
MRT_{last}	Mean residence time up to last measurable concentration
$MRT_{0\text{-}inf}$	Mean residence time extrapolated to infinity
NOAEL	No observed adverse effect level
[redacted]	[redacted]
[redacted]	[redacted]
OTC	Over-the-counter
PD	Pharmacodynamics
[redacted]	[redacted]
PK	Pharmacokinetics
PO	By mouth
PT	Preferred term
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction
RA	Rheumatoid arthritis
RASF	Rheumatoid arthritis synovial fibroblasts
Rb	Retinoblastoma protein
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SDAI	Simplified disease activity index
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reactions
t_{max}	Time of maximum plasma concentration determined directly from the concentration-time profile
TNF	Tumor necrosis factor
$t_{½}$	Terminal elimination half-life calculated

Abbreviations	Definition
ULN	Upper limit of normal
USA	United States of America
WOCBP	Women of childbearing potential

11 References

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