Cover page

Statistical Analysis Plan

Study ID: TCK-276-102

Study 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

NCT number: 05437419

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Teijin America, Inc.

[redacted]

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TCK-276-102

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

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SPONSOR SIGNATURE PAGE

This document has been approved and signed electronically on the final page by the following:

Approved by: [redacted]

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	[redacted]	New document
1.1	[redacted]	Updated dose strength to 175 mg throughout the document Update the unit of CRP from mg/dL to mg/L, accordingly, SDAI = SJC + TJC +PGA + EGA + 0.1*CRP DAS 28 CRP = 0.56× √ (TJC) + 0.28× √ (SJC) + 0.36×LN((CRP)+1) +0.14*×(PGA)+0.96 Added line in section 4.13.8 "If any of the elements are missing, then the corresponding parameter will be considered as missing." to handle the parameter in case of missing elements. Removed inactive URL link of DAS28 ESR
20	Date of last signature	Final

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
ACR	American College of Rheumatology
AE	Adverse event
Ae	Amount of study drug excreted unchanged in the urine
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from pre-dose (time 0) extrapolated to infinite time
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve up to last measurable concentration
AUC_{tau}	Area under the plasma concentration-time curve over a dosing interval
BDRM	Blinded data review meeting
BL	Biostatistician Lead
BLQ	Below the lower limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CCL2	C-C motif chemokine ligand 2
CDAI	Clinical disease activity index
CI	Confidence interval
CL/F	Apparent total body clearance, determined for parent only
C_{last}	Last observed quantifiable concentration at t_{last}
CL_r	Renal clearance of drug from plasma
C_{max}	Maximum plasma concentration determined directly from the concentration-time profile
COMP	Cartilage oligomeric matrix protein
CPMS	Clinical Pharmacology, Modeling, and Simulation

Abbreviation/Acronym	Definition/Expansion
CS	Clinically significant
CSR	Clinical Study Report
C_{trough}	Concentration in a dosing period defined as the pre-dose concentration of the day
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CXCL10	C-X-C motif chemokine ligand 10
DAS28	Disease activity score 28
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EGA	Evaluator Global Assessment (Provider global score)
EOS	End of study
Fe	Percentage of study drug excreted unchanged in the urine
Fe%	Urinary cumulative excretion as % of unchanged drug
GM-CSF	Granulocyte macrophage colony stimulating factor
HAQ	Health Assessment Questionnaire
HBc	Hepatitis B core
GM-CSF	Granulocyte macrophage colony stimulating factor
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed consent form
IGRA-TB	Interferon gamma release assay for tuberculosis
IL-6	Interleukin-6
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMP-3	Matrix metalloproteinase-3

Abbreviation/Acronym	Definition/Expansion
MR	Molar metabolic ratio
MRT	Mean residence time
MRT_{last}	Mean residence time up to last measurable concentration
$MRT_{0\text{-}inf}$	Mean residence time extrapolated to infinity
NC	Not calculated
NCS	Not clinically significant
NR	Not reportable
NS	No sample
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PGA	Patient Global Assessment(or Patient Global Score)
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PT	Preferred term
QD	Once daily
QTc	corrected QT interval
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
RA	Rheumatoid arthritis
R_{acc}	Accumulation ratio
RAN	Randomized Analysis Set
RTF	Rich text format
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation
SDAI	Simplified disease activity index

Abbreviation/Acronym	Definition/Expansion
SI	Standard international
SJC	Swollen Joint Count
SoA	Schedule of Assessment
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TEMA	Treatment-emergent markedly abnormal
TJC	Tender Joint Count
t_{last}	Time of last observed quantifiable concentration
t_{max}	Time of maximum plasma concentration determined directly from the concentration-time profile
TNF	Tumor necrosis factor
V_{ur}	Measured volume of urine collected during each collection interval
V_z/F	Apparent volume of distribution based on terminal phase, determined for parent only
WHO-DD	World Health Organization - Drug Dictionary
λ_z	Terminal elimination rate constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of Study TCK-276-102, 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.

The content of this SAP is based on following study documents:

- Study TCK-276-102 protocol Final Version 3.0 12 Dec 2022.
- Electronic Case Report Form (eCRF) Version 27.0 [redacted].

This SAP will be finalized prior to database lock. Any changes after the finalization of this SAP will be documented in Statistical Method Modification Form.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

Objectives	Endpoints
• 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

2.2 Secondary Objective(s)

Objectives	Endpoints
• 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) ○ 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.

2.3 Exploratory Objective(s)

Objectives	Endpoints
• 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)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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.

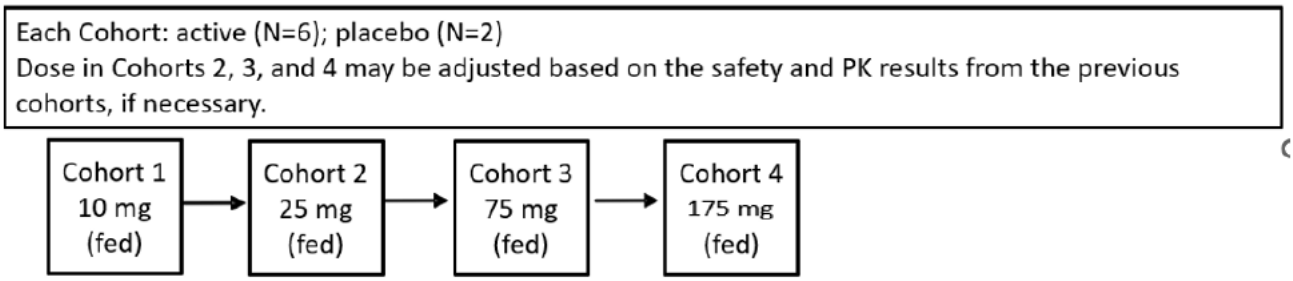
A total of thirty-two (32) patients with RA will be enrolled in this clinical study. This MAD study will consist of 4 cohorts of 8 patients (6 active treatment and 2 matching placebo, or a 3:1 ratio), each receiving an oral dose of TCK-276 or matching placebo for 7 days (once daily [QD] under fed condition). Each cohort will be divided into 2 subgroups to implement the sentinel dosing approach. Within each 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 subgroup following a decision by the Investigators based on all available safety data from the sentinel patients up to 48 hours post-dose.

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	175 mg TCK-276 (N = 6)	Placebo (N = 2)

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 175 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 2,355 ng·h/mL, which is set taking monkey testicular toxicity into consideration.

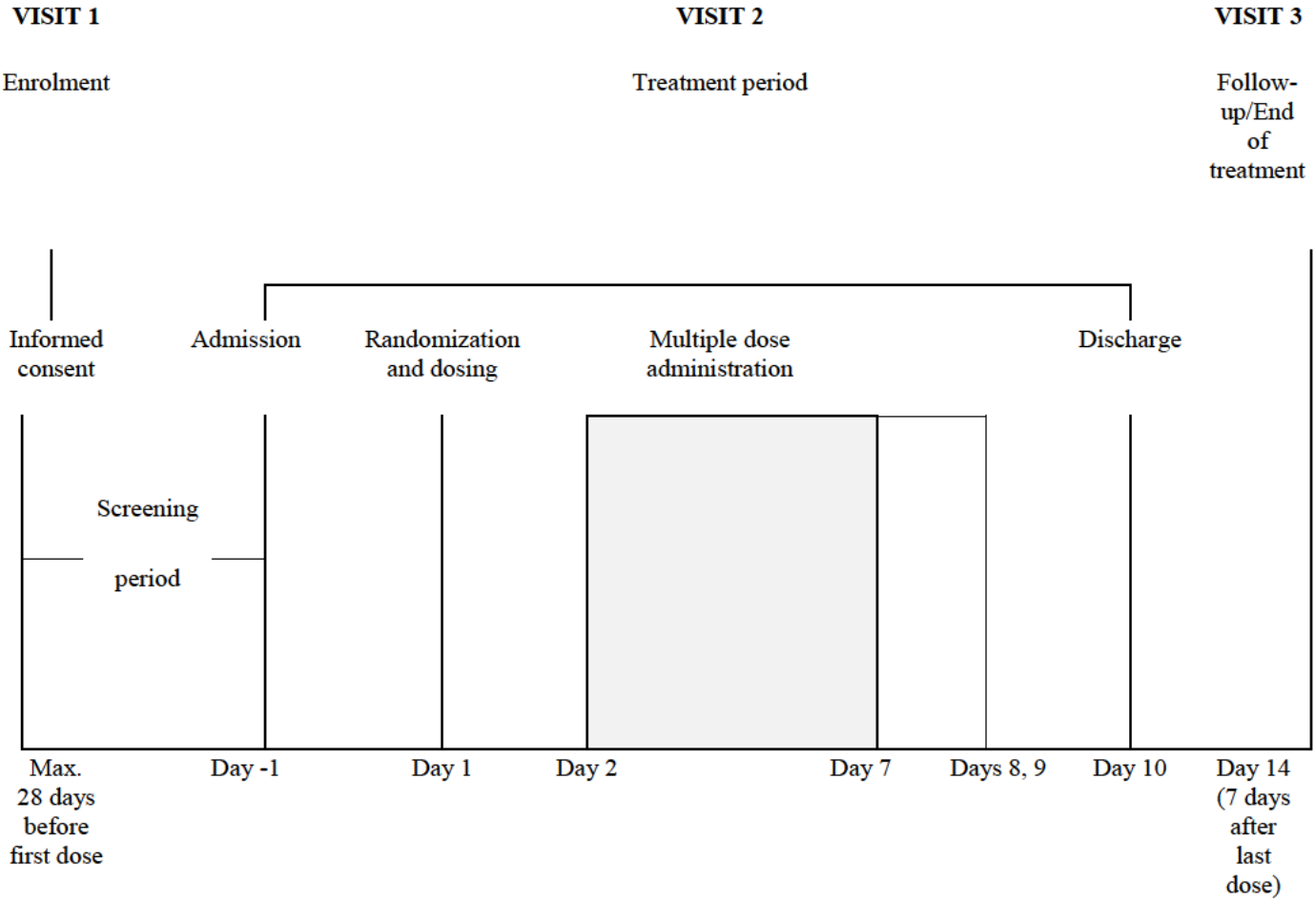
Dose escalation will only be allowed after blinded assessment of all safety, tolerability, and PK data up to Day 10 from each previous cohort evaluated by Investigators, Medical Monitor, and Sponsor representatives during the Safety Review Committee (SRC) meeting.

Figure 3-1 Study Design



N = number of patients; PK = pharmacokinetics

Figure 3-2 Study Flow Chart – Multiple Ascending Dose Design



3.2 Endpoints and Associated Variables

3.2.1 Safety Variables

The following safety and tolerability variables will be recorded at regular intervals during the study:

- Vital signs (supine blood pressure [BP] and pulse rate, tympanic (ear) body temperature, 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

3.2.2 Pharmacokinetic Variables

Pharmacokinetic concentration data will be obtained at time point(s) described in the protocol version 2.0 [redacted] as follows:

Blood sample for PK sample analysis to determine parent (TCK-276) and its metabolite (TEI-W00595) concentrations and for possible future metabolite assessments will be collected at the time points detailed in the Schedule of Assessments 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).

Blood for the PK sample analysis 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, 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 cohorts. The last dose will be administered on Day 7.

Urine samples for the analysis of TCK-276 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. Volumes of urine collected in each time window will also be recorded in the clinical database. Urine collection intervals may be adjusted based on the PK results obtained from the previous cohorts, e.g., if plasma PK sampling times are adjusted, the urine sampling times will be updated.

Derivation of PK parameters will be the responsibility of Clinical Pharmacology, Modeling and Simulation (CPMS) group, [redacted].

If calculable, the following PK Day 1 parameters listed in Table 3-1 will be determined for parent, TCK-276 and metabolite, TEI-W00595, in plasma following first oral dose administration.

Table 3-1 Plasma Pharmacokinetic Parameters of TCK-276 and TEI-W00595 After First Dose Administration

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration determined directly from the concentration-time profile
DNC_{max}	CmaxD	CMAXD	Dose-normalized C_{max}
t_{max}	Tmax	TMAX	Time of maximum plasma concentration corresponding to occurrence of C_{max}
λ_z	Lambda_z	LAMZ	Terminal elimination rate constant
AUC_{tau}	AUC_TAU	AUCTAU	Since dosing interval or tau equals 24 hours, area under the curve from time 0 to 24 hours (AUC_{0-24h}) will be calculated and will be referred to AUC_{tau} for Day 1
$DNAUC_{tau}$	AUC_TAUD	AUCTAUD	Dose normalized AUC_{tau}
AUC_{0-t}	AUClast	AUCLST	AUC from time zero to the last quantifiable concentration
$DNAUC_{0-t}$	AUClast_D	AUCLSTD	Dose-normalized AUC_{0-t}
AUC_{0-inf}	AUCINF_obs	AUCIFO	AUC from time zero extrapolated to infinity
$\%AUC_{ex}$	AUC_%Extrap_obs	AUCPEO	Percentage of AUC_{0-inf} obtained by extrapolation beyond t_{last}
$DNAUC_{0-inf}$	AUCINF_D_obs	AUCIFOD	Dose-normalized AUC_{0-inf}
MRT_{last}	MRT_{last}	MRTEVLST	Mean residence time up to last measurable concentration
MRT_{0-inf}	MRTINF_obs	MRTEVIFO	Mean residence time extrapolated to infinity

Parameter	WNL Name	CDISC Name	Definition
$t_{½}$	HL_Lambda_z	LAMZHL	Apparent terminal elimination half-life
CL/F	Cl_F_obs	CLFO	Apparent clearance following oral administration, determined for parent only
V_z/F	Vz_F_obs	VZFO	Apparent volume of distribution during terminal phase, determined for parent only
MR_{Cmax}	MRCmax	MRCMAX	Molar metabolic ratio based on C_{max} of parent and metabolite
MR_{AUCtau}	MRAUCtau	MRAUC	Molar metabolic ratio based on AUC_{tau} of parent and metabolite
MR_{AUC0-t}	MRAUClast	MRAUCLS	Molar metabolic ratio based on AUC_{0-t} of parent and metabolite
$MR_{AUC0-inf}$	MRAUCINF	MRAUCIN	Molar metabolic ratio based on AUC_{0-inf} of parent and metabolite

If calculable, the PK Day 7 parameters listed in Table 3-2 will be calculated for parent, TCK-276 and metabolite, TEI-W00595 in plasma following once daily oral dose administration after last dose administration on Day 7:

Table 3-2 Plasma Pharmacokinetic Parameters of TCK-276 and TEI-W00595 After Last Dose of Daily Dose Administration

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration determined directly from the concentration-time profile
DNC_{max}	CmaxD	CMAXD	Dose-normalized C_{max}
t_{max}	Tmax	TMAX	Time of maximum plasma concentration corresponding to occurrence of C_{max}
λ_z	Lambda_z	LAMZ	Terminal elimination rate constant
AUC_{tau}	AUC_TAU	AUCTAU	Since dosing interval or tau equals 24 hours, area under the curve from time 0 to 24 hours (AUC_{0-24h}) will be calculated and will be referred to AUC_{tau} for Day 7
$DNAUC_{tau}$	AUC_TAUD	AUCTAUD	Dose-normalized AUC_{tau}
AUC_{0-t}	AUClast	AUCLST	AUC from time zero to the last quantifiable concentration
$DNAUC_{0-t}$	AUClast_D	AUCLSTD	Dose-normalized AUC_{0-t}
AUC_{0-inf}	AUCINF_obs	AUCIFO	AUC from time zero extrapolated to infinity
$\%AUC_{ex}$	AUC_%Extrap_obs	AUCPEO	Percentage of AUC_{0-inf} obtained by extrapolation beyond t_{last}
$DNAUC_{0-inf}$	AUCINF_D_obs	AUCIFOD	Dose-normalized AUC_{0-inf}
MRT_{0-inf}	MRTINF_obs	MRTEVIFO	Mean residence time extrapolated to infinity
$t_{½}$	HL_Lambda_z	LAMZHL	Apparent terminal elimination half-life
CL/F	Cl_F_obs	CLFO	Apparent clearance following oral administration, determined for parent only

Parameter	WNL Name	CDISC Name	Definition
V_z/F	Vz_F_obs	VZFO	Apparent volume of distribution during terminal phase, determined for parent only
MR_{Cmax}	MRCmax	MRCMAX	Molar metabolic ratio based on C_{max} of parent and metabolite
MR_{AUCtau}	MRCAUCtau	MRCAUC	Molar metabolic ratio based on AUC_{tau} of parent and metabolite
MR_{AUC0-t}	MRAUClast	MRAUCLS	Molar metabolic ratio based on AUC_{0-t} of parent and metabolite
$MR_{AUC0-inf}$	MRAUCINF	MRAUCIN	Molar metabolic ratio based on AUC_{0-inf} of parent and metabolite
C_{trough}	Ctrough	CTROUGH	Concentration in a dosing period defined as pre-dose concentration of the day on Day 2 to Day 7, and 24 after Day 7 dosing
$R_{acc}(C_{max})$	ARCMAX	ARCMAX	Accumulation ratio based on C_{max}
$R_{acc}(AUC_{tau})$	ARAUC	ARAUC	Accumulation ratio based on AUC_{tau}

Additional PK parameters will be determined and reported as needed.

The concentration of TCK-276 as well as volume of urine collected in each collection interval (V_{ur}) will be used to calculate amount of TCK-276 in each collection interval and to determine the urine PK parameters listed in Table 3-3.

Table 3-3 Urine Pharmacokinetic Parameters

Protocol Parameter	WNL Name	CDISC Name	Definition
Ae	Amount Recovered	RCAMINT	Amount of unchanged drug excreted in urine in each interval collection (e.g. Ae_{0-6}, Ae_{6-12}, Ae_{12-24} after Day 1 and Day 7 dosing, additionally Ae_{24-48} and Ae_{48-72} following Day 7 dosing). In addition, cumulative amount excreted after each collection interval will also be determined (e.g. Ae_{0-6}, Ae_{0-12}, Ae_{0-24} after Day 1 and Day 7 dosing, additionally Ae_{0-48} and Ae_{0-72} following Day 7 dosing)
Fe	Percent_Recovered	RCPCINT	Urinary cumulative excretion as % of unchanged drug up to 24 hours following Day 1 and Day 7 dosing, and additionally up to 72 hours following Day 7 dosing (e.g. Fe_{0-6}, Fe_{0-12}, Fe_{0-24} after Day 1 and Day 7 dosing, additionally Fe_{0-48} and Fe_{0-72} following Day 7 dosing).
CL_r	CLR@	RENALCL	Renal clearance of the drug from plasma following Day 1 and Day 7 dosing

3.2.3 Efficacy Variables

Not Applicable

3.2.4 Pharmacodynamic Variables

Not Applicable

3.2.5 Immunogenicity Variables

Not Applicable

3.2.6 Exploratory Variables

The following exploratory disease activity parameters for RA will be assessed on day 1 and day 7:

- 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 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with [redacted].

4.2 General Presentation Considerations

This section is not applicable to PK data.

4.2.1 Treatment

Cohort 1: 10 mg TCK-276

Cohort 2: 25 mg TCK-276

Cohort 3: 75 mg TCK-276

Cohort 4: 175 mg TCK-276

Pooled Placebo

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	175 mg TCK-276 (N = 6)	Placebo (N = 2)

4.2.2 Study Day

Study days will be numbered relative to the first day of study drug administration.

- If the date of event is before the study drug administration, then:

  Study day = (Date of measurement – Date of study drug administration [i.e. Day 1])

- If the date of event is on or after the study drug administration, then:

  Study day = (Date of measurement – Date of study drug administration [i.e. Day 1]) + 1

4.2.3 End of Study

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 Table 6-1 Schedule of Assessments.

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

4.2.4 Baseline

Baseline value is defined as the last non-missing observation before the first administration of study drug.

No imputation will be done for missing baseline value for derivation of change from baseline or summary tables and shift tables.

4.2.5 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment

Repeat, retest, and unscheduled assessment will not be considered for the calculation of summary statistics and figures, unless assessment qualifies as baseline.

Average of controlled and planned (scheduled) assessment will be considered for the calculation of summary statistics and figures, if more than one controlled/planned assessment will be performed at a specific time point.

4.2.6 Summary and Representation of Data

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.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics.

Percentages will be presented to one decimal place for safety outputs and two decimal places for exploratory outputs. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Percentage will be presented as whole number if count is 100.

4.2.7 On-treatment assessment/event

The overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to before date of admission

2. ***on-treatment period***: from date of admission (Day -1) to discharge from site (11 days i.e., from Day -1 to Day 10)
3. ***post-treatment period***: from after date of discharge from the Site up to follow-up/End of treatment visit. (7 days after the last dose)

4.3 Software

All report outputs will be produced using SAS® version 9.4 or later in a secure and validated environment.

The PK analyses will be conducted using Phoenix® WinNonlin (WNL) version 8.3 or later in a secure and validated environment.

All report outputs will be provided to the Sponsor in Microsoft Word document/RTF format.

4.4 Study Patients

4.4.1 Analysis Sets

Randomized Population (RAN): All patients that signed informed consent form and assigned randomization number.

Safety Population (SAF): All randomized patients who received at least one dose of study drug (active/placebo).

PK Population (PKAS): 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 at least one of the evaluable exploratory assessment data.

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.

4.4.2 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from randomization to study and treatment completion.

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 treatment, and the number and percentage of patients who were withdrawn (including reasons for withdrawal) from study and treatment. Disposition data will be presented based on RAN.

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

A by-patient listing of study and treatment discontinuation will be presented for the RAN. The listing will include the date of study exit, duration of treatment and reason for study treatment discontinuation.

A by-patient listing of informed consent response will be provided.

4.4.3 Protocol Deviations

All protocol deviations are predefined in the separate document, Protocol Deviation Specification.

4.4.3.1 Protocol Deviations with Non-PK Implications

The defined protocol deviations will be collected during the study period by site monitor/clinical team and programming team. All deviations related to study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment, and handling of the patient's rights will be described.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited to:

- Emetic episode in case of orally administered study drug
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol
- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s)
- Food intake deviations (not completely consumed or consumed outside of time allowed)

Protocol deviations (mentioned in Sections 4.4.3.1 and 4.4.3.2) and analysis population will be reviewed in the blinded data review meeting (BDRM) to decide inclusion or exclusion of patient(s) from analyses sets. Decisions regarding the exclusion of patients and/or patient data from analyses will be made prior to database lock and will be documented and approved, however, exclusion of patients or individual PK parameters will be decided after database lock after review of the calculable PK parameters, and any PK data excluded from summary tables/plots will be appropriately commented upon in the PK Listings.

A by-patient listing of major and minor protocol deviations will be provided including patient identifier; exclusion from specific analysis sets; and protocol deviation classification, and protocol deviation description and exclusion from specific analysis sets.

Protocol deviations related to Covid-19 will be listed separately.

4.5 Demographics and Anthropometric Information and Baseline Characteristics

The demographic and anthropometric variables (age, race, ethnicity, sex, height, body weight, body mass index [BMI] will be summarized for all patient by cohort, treatment and overall.

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight, and BMI) will be listed by patient for the SAF.

Age, height, BMI, weight will be summarized using the n, mean, SD, minimum, median, and maximum. The count and percentage will be computed for sex, race, and ethnicity.

A by-patient listing of history of substance abuse and history of RA and related surgical history will be provided.

4.6 Medical and Surgical History

Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Version 25.0 and assigned to a System Organ Class (SOC) and Preferred Term (PT).

A by-patient listing for medical and surgical history 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) will be provided, and summarized for the SAF.

4.7 Prior and Concomitant Medications

Prior and Concomitant Medication:

Medications will be considered as prior if it is started and stopped prior to the first dose of study drug.

Medications will be considered as concomitant if they are taken after first dosing (including medications that started prior to dosing and continued after)

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

By-patient listings of prior and concomitant medications including the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration, and indication will be provided, by WHO DD terms for the SAF.

Prior Medications and concomitant medication will be summarized by WHO DD terms for the SAF.

4.8 Treatment Exposure and Compliance

4.8.1 Treatment Exposure

A by-patient listing of patient exposure to study drug will be generated. The listing will include date and time of administration.

4.8.2 Compliance

A by-patient listing of treatment compliance will be provided.

Overall Treatment Compliance (%) will be defined as percentage of total dose taken during the study divided by the expected total dose in mg.

4.9 Analysis Supporting Primary Objective(s)

Not Applicable

4.10 Analysis Supporting Secondary Objective(s)

Not Applicable

4.11 Efficacy Evaluation

Not Applicable

4.12 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis

4.12.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic Plasma concentration data for TCK-276 and TEI-W00595, will be listed by cohort/treatment/Day and patient for the PKAS. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR) as appropriate and considered excluded from PK analysis.

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of patients in PKAS), n (number of patients with non-missing values), and n(BLQ) (the number of patients with BLQ samples).

Concentration for TCK-276 and TEI-W00595 will be summarized by cohort/treatment/Day, and nominal timepoint for the PKAS. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum, and maximum values.

For summary concentration tables, all BLQs will be considered zero, and the number of BLQs and quantifiable concentrations at each scheduled time point will be reported. Summary Statistics will not be calculated if quantifiable concentrations at a scheduled time point is <3 and will be reported as not calculated (NC).

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of patient level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations (Listings)	*n* s f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s f. as supplied by bioanalytical laboratory
Mean/SD/Median/Geomean	3 s.f.
CV%/gCV%	1 d.p.
N/n	Whole number

s f = significant figures, d.p. = decimal place

For the final plasma concentration PK summary tables and figures, if the 0.25 and 0.5 h samples are collected outside +/- 5 minutes time window, the concentration will be flagged and not included in the concentration summary tables and mean concentration-time plots. For 1 to 48 h sample, if the sample is collected outside 10% time deviation of the scheduled time or outside +/- 30 minutes time window, it will be flagged and not included in the concentration summary tables and mean

concentration-time plots. For 72 h sample, if the sample is collected outside +/- 60 minutes time window, it will be flagged and not included in the concentration summary tables and mean concentration-time plots.

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean. The arithmetic mean will not be calculated if quantifiable concentrations at a scheduled time point is <3 and will not be plotted in Figures. For log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).

For individual linear/linear and log/linear graphs, all BLQ values will be substituted as follows:

- BLQs at the beginning of a patient profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a patient profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing.
- If there are quantifiable concentrations following consecutive BLQs in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.

To visualize patient-level concentrations and the comparison between cohort/treatment, the descriptive PK graphs listed below will be generated.

- Figure x.x.x: Individual patient profiles for TCK-276 and TEI-W00595 Plasma Concentration Time Data for Day 1 and Day 7 dosing by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[4 profiles for every individual, Day 1 parent, Day 7 parent, Day 1 metabolite, Day 7 metabolite)]*
- Figure x.x.x : Overlaid individual patient profiles for TCK-276 Plasma Concentration Time Data for Day 1 and Day 7 dosing by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Dose 1 Days 1-2, Dose 7 Days 7-10)]*
- Figure x.x.x : Overlaid individual patient profiles for TEI-W00595 Plasma Concentration Time Data for Day 1 and Day 7 dosing by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots with Dose 1 Days 1-2, Dose 7 Days 7-10]*
- Figure x.x.x: Overlaid individual patient profiles for TCK-276 Plasma Trough Concentration Time Data by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Day 2 – Day 8]*
- Figure x.x.x: Overlaid individual patient profiles for TEI-W00595 Plasma Trough Concentration Time Data by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Day 2 – Day 8]*

- Figure x.x.x : Mean (+ SD) TCK-276 Trough Plasma Concentration Time Data — (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Day 2 – Day 8 for all doses* on one plot*)*
- Figure x.x.x : Mean (+ SD) TEI-W00595 Trough Plasma Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Day 2 – Day 8* for all doses *on one plot)*
- Figure x.x.x : Mean (+ SD) TCK-276 Plasma Concentration Time Data for Day 1 and Day 7 by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) – *[Plots for Day 1 all doses, Day 7 all doses and Plots for from Day 1 to Day 7)*
- Figure x.x.x : Mean (+ SD) TEI-W00595 Plasma Concentration Time Data for Day 1 and Day 7 by Dose – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Day 1 all doses, Day 7 all doses and Plots for from Day 1 to Day 7)*
- Figure x.x.x : Mean (+ SD) TCK-276 Plasma Concentration Time Data for Day 1 and Day 7 by cohort – (Linear Scale and Semi-Logarithmic Scale) (PKAS) – *[Plots for Day 1; Day 7; Day 1, Day 7 and trough day 3-6)*
- Figure x.x.x : Mean (+ SD) TEI-W00595 Plasma Concentration Time Data for Day 1 and Day 7 by cohort – (Linear Scale and Semi-Logarithmic Scale) (PKAS) *[Plots for Day 1; Day 7; Day 1, Day 7 and trough day 3-6)*

Figures will be generated in black and white using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (i.e. do not use an ordinal scale).

4.12.2 Pharmacokinetic Parameters

PK parameters will be provided by CPMS group. PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin® Version 8.3 or higher following these guidelines:

- Actual time from dose will be used in the calculation of all derived pharmacokinetic parameters, except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- There will be no imputation of missing data.
- Handling of BLQ samples for derivation of plasma PK parameters after multiple dose administration
    - BLQs for Day 1 at the beginning of a patient profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero
    - BLQs on subsequent dosing days, and BLQs in the absorption phase will be substituted by zero before the calculation of the PK parameters
    - BLQ values between non-BLQ concentrations will be considered missing
    - Terminal BLQs (at the end of patient profile) will be set to missing
- If urinary concentration is BLQ or if urine volume is not collected, amount of unchanged drug recovered in urine (A_e) will be defined as NC

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 4-1.

Table 4-1 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, t_{max}, $C_{trough,}$	Obtained directly from the observed concentration-time data. If multiple t_{max} values are observed the earliest value will be reported.
AUC_{0-t}	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by the linear trapezoidal linear interpolation rule. The AUC_{0-t} is the sum of areas up to the time of the last quantifiable sample: $AUC_{0-t}=\int_0^t C_{last} * dt$ where C_{last} is the last observed quantifiable concentration.
AUC_{tau}	The AUC over the dosing interval (24 hours) will be determined for multiple dose studies using the trapezoidal rule, as stated above.
AUC_{0-inf}	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC_{0-inf} = AUC_{0-t}+\frac{C_{last}}{\lambda_z}$ where C_{last} is the last observed quantifiable concentration.
%AUC_{ex}	The percentage of AUC_{0-inf} obtained by extrapolation will be calculated as follows: $\%AUC_{ex}=\frac{AUC_{0-inf} - AUC_{0-t}}{AUC_{0-inf}} x100$.
λz and t½	1. The apparent terminal phase rate-constant (λz) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Lambda z (λ_z) and other λ_z-related parameters (i.e. t½, AUC_{0-inf}, CL/F, MRT_{0-inf}, and V_z/F) will be flagged in listings and excluded accordingly from summary tables and statistical analysis of PK parameters, if the adjusted correlation coefficient (R^2 adjusted) is <0.8, and/or the interval used to determine λz is <1.3 times the half-life and/or %AUC_{ex} is >30%, unless otherwise determined by PK Scientist's best knowledge and judgment or if instructed by the Sponsor. 6. The t½ will be calculated as follows: $t½ = \ln 2/\lambda z = 0.693/\lambda z$ 7. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings with a footnote and be identified in the study report with a rationale for exclusion.
CL/F	Apparent clearance after 1st dose will be calculated as follows: $CL/F = \frac{Dose}{AUC_{0-inf}}$ Apparent clearance (CL/F) following oral dosing will be calculated similarly for Day 7 where AUC_{tau} will be the denominator, assuming steady state has been achieved then.

Parameter	Guideline for Derivation
MRT_{last}	MRT_{last} will be calculated as follows: $MRT_{last} = AUMC_{last}/AUC_{last}$ (Day 1 only)
$MRT_{0\text{-}inf}$	$MRT_{0\text{-}inf}$ will be calculated as follows: Day 1: $AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}$ Day 7: $(AUMC_{tau} + \tau*(AUC_{0\text{-}inf} - AUC_{tau}))/ AUC_{tau}$ Where AUMC is the area under the moments curve and τ is the dosing interval.
V_z/F	Volume of distribution at terminal phase on Day 1will be calculated as follows: $V_z/F = \frac{Dose}{\lambda_z \times AUC_{0\text{-}inf}} = (CL/F)/ \lambda_z$ Likewise, if derived for Day 7 or steady, AUC_{tau} will be used.
CL_r	Renal clearance will be calculated from the ratio of the appropriate values for urinary recovery and area under the concentration-time curve, where x will be 24 (Day 1) and 72 (Day 7) hours: $CL_r = \frac{Ae_{(0-x)}}{AUC_{(0-x)}}$
R_{acc}	Accumulation ratio, calculated from comparison of single dose (Day 1) and steady state (Day 7) data: $R_{acc}(AUC_{tau}) = \frac{Steady\ state\ AUC_{tau}}{Single\ dose\ AUC_{tau}}$ $R_{acc}(C_{max}) = Steady\ state\ C_{max}/\ Single\ dose\ C_{max}$
A_e	Amount of unchanged drug recovered in urine is calculated as $A_e = Urine\ drug\ concentration * urine\ volume$ This is calculated for each urine collection interval and then summed for the cumulative A_e.
$F_e\%$	The percent of drug recovered in urine is calculated as $F_e = 100 * A_e/Dose$ This is calculated for each urine collection interval and then summed for the cumulative $F_e\%$.
MR for AUC	Metabolite molar ratio for Day 1 and Day 7 will be calculated as $MR\ for\ AUC_{0\text{-}inf} = (AUC_{0\text{-}inf}\ metabolite/AUC_{0\text{-}inf}\ parent) * (MWparent/MWmetabolite)$ Similarly, metabolite molar ratios will be collected for other AUCs defined earlier in this SAP. Metabolite molar ratios will be calculated based on molecular weight of [redacted] for parent, TCK-276 and [redacted] for metabolite TEI-W00595.

Parameter	Guideline for Derivation
MR for C_{max}	Metabolite molar ratio for Day 1 and Day 7 will be calculated as *MR for* C_{max} = *(*C_{max} *metabolite/* C_{max} *parent) * (MWparent/MWmetabolite)* Metabolite molar ratios will be calculated based on molecular weight of [redacted] for parent, TCK-276 and [redacted] for metabolite TEI-W00595.
DNC_{max}, $DNAUC_{0\text{-}t}$, $DNAUC_{0\text{-}inf}$, $DNAUC_{tau}$	Parameter value divided by dose

PK Parameters Listings:

PK parameters will be listed by patient for the PK Population. PK parameters that will be flagged and/or excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with the reason for flagging/exclusion.

PK Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by cohort/treatment and Day for the PK population. Tabular summaries for PK parameters will report N (number of patients who received treatment) and n (number of patients with non-missing PK parameter). Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. For t_{max}, only N, n, arithmetic mean, SD, CV%, median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of patient level PK parameters and summary tables of PK parameters are as follows:

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s f.
Directly Derived Individual parameters (e.g., C_{max}, C_{trough})	*n* s f. as supplied by the analytical laboratory but not more than 3 s f.
Minimum and Maximum	3 s f.
Mean/SD/Median/Geomean	3 s f.
CV%/gCV%	1 d.p.
CI	3 s f.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	2 d.p
t_{max} median only	2 d.p

s f = significant figures, d.p. = decimal place

PK Parameter Figures:

Following figures will be created:

- Dose-normalized TCK-276 Plasma PK Parameter (dose-normalized C_{max}, all dose-normalized AUC) against Dose of TCK-276 scatter plot of individual values and line plot of geometric mean values
- Log-transformed TCK-276 PK Parameter (C_{max}, all AUCs) against the Log transformed Dose of TCK-276 based on power model
- Overlaid Individual Urinary Cumulative Excretion Rate (%) of TCK-276 versus End of Collection Interval Time Point for Day 1 and Day 7 by Dose *[Plots for Day 1 all doses and Day 7 all doses]*
- Mean (+ SD) Urinary Cumulative Excretion Rate (%) of TCK-276 versus End of Collection Interval Time Point for Day 1 and Day 7 *[Plots for Day 1 all doses and Day 7 all doses]*

4.12.3 Statistical Analysis of Pharmacokinetic Parameters

❖ **Assessment of Dose Proportionality**

Power model is used for assessment of dose proportionality.

- Power model:
  - Power model using linear regression method:

Dose proportionality will be assessed for C_{max}, AUC_{tau}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ on Day 1 and Day 7 using the PKAS who received single or multiple doses of TCK-276. PK parameters will be used to perform a LS linear regression analysis, using the formula ln_pkvar=A× ln_dose + B, where 'ln pkvar' represents the natural log transformed C_{max} AUC_{tau}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ parameters and 'ln_dose' represents the natural log-transformed dose. An estimate of the slope and intercept of the regression line and corresponding 95% CI will be obtained.

The following SAS code will be used:

```
ODS OUTPUT parameterestimates=est FitStatistics=fit;
PROC REG DATA = PP ALPHA=0.05 PLOTS=ALL;
    BY PARAMCD PARAM;
    MODEL LNAVAL=LNDOS/CLB;
RUN;
```

where:

LNAVAL: natural log-transformed PK parameter

LNDOS: natural log-transformed dose level of <drug>

PARAM: PK parameter

If the 95% confidence interval (CI) range for the slope includes 1 and the lack of fit test is not significant (p-value < 0.05), the relationship between dose and the PK parameter will be concluded to be dose proportional for the dose range studied.

If the 95% CI range for the slope does not include 1 or the lack of fit test is significant (p-value < 0.05), then additional dose proportionality assessments using above power model with narrower dose range will be performed by sequentially decreasing the number of doses either from higher or lower end of dose range studied as shown in below tabular manner for the respective assessments and combinations. The doses for the assessments must be sequential and include at least 3 doses. All the possible combinations of sequential ascending doses in a certain number of doses will be applied for the assessments. The additional proportionality assessments will be repeated until dose proportionality is found in any dose ranges (minimum 3 doses) and the lack of fit test is not significant.

Table 4-2 Dose Proportionality Assessments in 2 round as shown below

Round	Combination	Range of Doses (in mg)	Assessment
1st	With all four-dose studied	10, 25, 75, 175	If no dose proportionality is shown, perform 2nd Round
2nd	1st – with 3 doses	10, 25, 75	Stop the assessment at this round even if none of the combinations shows dose proportionality.
	2nd – with 3 doses	25, 75, 175	

Note: If all 4 doses cannot be administered because of protocol defined dose escalation stopping criteria, dose proportionality will be appropriately updated.

4.12.4 Pharmacodynamic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacodynamic Parameters

Not Applicable

4.13 Safety Evaluation

All safety summaries and analyses will be based upon the SAF as defined in Section 4.4.1.

All summaries will be provided by cohort and treatment.

Placebo across cohorts will be pooled.

4.13.1 Adverse Events

All outputs for AEs/treatment-emergent adverse events (TEAEs) will be based on the SAF unless specified separately in TLF shells. AEs are to be classified by using Medical Dictionary for Regulatory Activities (MedDRA®), Version 25.0 or higher and assigned to a System Organ Class (SOC) and Preferred Term (PT).

All AE will be summarized by MedDRA terms and treatment groups. It will include evaluation of the number of AEs and the number and percentage of patients reporting at least one AEs.

Summaries of AEs will include the following:

- Incidence of AEs - Overview (by cohort/treatment and overall)
- Incidence of TEAEs (by cohort/treatment and overall, SOC, and PT)
- Incidence of TEAEs by relationship (by cohort/treatment and overall, SOC, and PT)
- Incidence of TEAEs by maximum severity (mild/moderate/severe, by cohort/treatment and overall, SOC, and PT)
- Incidence of TEAEs leading to discontinuation of study treatment
- Incidence of SAEs
- Incidence of TEAEs Related to IMP by maximum severity (mild/moderate/severe, by cohort/treatment and overall, SOC, and PT)

Summary tables will contain counts of patients, percentages of patients in parentheses, and the number of events where applicable. A patient who has multiple events in the same SOC and PT will be counted only once in the patient counts, but all events will be included.

All Adverse Events (AEs)

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, time from onset since last study drug administration, 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.

Treatment-emergent Adverse Event

A TEAE will be defined as any AE that emerge during treatment (i.e., AE which started after study drug administration or pre-existed that worsened in severity after study drug administration) and those will be analyzed for the purpose of safety analysis.

TEAEs will be summarized by SOC and PT, including the number and percentage of patients experiencing events, separately.

Severity

TEAEs will be summarized by SOC, PT, and severity, including the number and percentage of patients experiencing events. If a patient reports the same TEAE more than once within that SOC and PT, the TEAE with the highest severity will be used in the corresponding severity summaries.

In summaries including severity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Subjects who experience the same event multiple times will be included in the most severe category. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

If severity is reported by Common Terminology Criteria for Adverse Events (CTCAE) grade, then summary of severity will be presented using CTCAE grade.

Relationship (Causality)

TEAEs will be summarized by SOC, PT, and causality, including the number and percentage of patients experiencing events. Relationship to study drug will be tabulated respectively. If a patient reports the same TEAE more than once within that SOC and PT, the TEAE with the worst-case relationship to study drug will be in summaries including relationship to study treatment, the following relationships will be summarized: 'Not related', 'Related'. Patients who experience the same event multiple times will be included in the most related category. Events with missing relationship will be considered as 'Related' to the last given study drug for summary purposes but recorded as missing in the listings.

Adverse Events of Special Interest (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:
- Interstitial lung disease: Pulmonary symptoms (dyspnea, pyrexia, and cough)
- Gastrointestinal toxicity: e.g., diarrhea, nausea, vomiting, and abdominal pain.

Adverse events of special interest (AESI) will be summarized by SOC and PT, including the number and percentage of patients experiencing events. Listing of AESI will be provided.

4.13.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Describe the listings that are to be provided. These may include the following listings:

- A by-patient listing of all SAEs

- A by-patient listing of all AES leading to discontinuation of study treatment

Listings should follow the format described for AEs in Section 4.13.1 if appropriate.

4.13.3 Clinical Laboratory Evaluation

Clinical laboratory test results of hematology, clinical chemistry, urinalysis, urinary drug screening, coagulation and serology will be provided by patient.

All TLFs will display only the standard international (SI) units after conversion by means of standard conversion factors.

Quantitative clinical laboratory variables, i.e., hematology, clinical chemistry, coagulation and urinalysis will be summarized using descriptive statistics (n, mean, SD, minimum, maximum and median) by cohort, treatment group and time-point. Additionally, a within-patient change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Baseline definition is defined in section 4.2.4.

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each time point according to the laboratory supplied reference ranges. For hematology , clinical chemistry, coagulation and urinalysis, shift tables will be presented showing the number and percentage of patients with shifts from baseline to each post dose time point. Tabulations will be presented by cohort and treatment group.

Measurements obtained at Screening will not be included in the shift tables and in the tabulations of descriptive statistics.

Measurements obtained prior to dosing in each period will be included in the tabulations for the treatment received in that specific treatment period.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by cohort, treatment group and time-point.

All laboratory data will be displayed in listings.

Laboratory abnormalities that are considered clinically significant (CS) are recorded in the database as AEs. Therefore, no tabulation of laboratory values meeting any CS criteria (except liver chemistry) will be presented as all relevant information will be presented in the AE summaries.

Results of pregnancy tests (females only), viral serology, covid-19 test, urine drug screening, cotinine test, and alcohol tests will be listed in other laboratory test.

4.13.4 Vital Signs

A by-patient listing of all vital sign measurements (including weight) and change from baseline will be presented.

Baseline is defined in section 4.2.4.

Measured (observed) values including changes from baseline will be summarized by cohort/ treatment and time point and by vital sign parameter (BP (systolic and diastolic [mmHg]), pulse rate(bpm), respiratory rate (breaths per minute), and body temperature (tympanic [ear] or non-contact infrared thermometers) (°C)).

Measurements obtained at screening will not be included in the tabulations of descriptive statistics.

4.13.5 ECG

Standard safety 12-lead ECGs will be performed as shown in the section 6.1.

The following ECG parameters will be recorded:

PR interval (msec)

QRS interval (msec)

RR interval (msec)

QT interval (msec)

QT interval corrected using the Fridericia correction formula (QTcF) (msec).

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

All ECG parameters will be listed by each patient and time point including changes from baseline.

Baseline is defined in section 4.2.4.

Descriptive statistics for observed values and changes from baseline will be presented by cohort and treatment group. A categorical QTc analysis will also be performed.

Measurements obtained at Screening will not be included in the shift tables and in the tabulations of descriptive statistics.

Measurements obtained prior to dosing in each period will be included in the tabulations for the treatment received in that specific treatment period.

A summary of the number and percentage of patients with QT/QTc intervals exceeding some predefined upper limits (eg, >450 msec, >480 msec, >500 msec for measured values as well as. >30 msec, >60 msec for changes from baseline) of ECG parameters (QT interval, QTcF and QTcB) will be displayed in a frequency table.

The listing of ECG abnormality will be presented separately.

4.13.6 Physical Examination

Physical examinations will be performed as shown in the section 6.1.

The full physical examination includes 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).

The brief physical examination includes an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory system.

Abnormal physical examination findings will be listed.

4.13.7 Other Analysis

Not Applicable

4.13.8 Exploratory Analysis

The following disease activity parameters for RA will be listed and summarized by descriptive statistics and displayed graphically as appropriate.

- 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 derivation of the above endpoints is as follow:

elements	CDAI	SDAI	DAS28 CRP	DAS28 ESR	ACR
Swollen Joint Count (SJC)	X	X	X	X	X
Tender Joint Count (TJC)	X	X	X	X	X
Patient Global Assessment (PGA or Patient global score)	X	X	X	X	X
Evaluator Global Assessment (EGA or Provider global score)	X	X			X
CRP (mg/L)		X	X		x (or ESR)
ESR (mm/hr)				X	x (or CRP)
Pain VAS					X
HAQ					X

Baseline (Day 1), Current value (Day 7) and CFB (Day 1 - Day 7) and %CFB ((Day 1-Day7)/Day1*100) of Disease activity data elements (numbers of SJC and TJC, PGA, EGA, CRP, ESR, pain VAS and HAQ-DI) scores will be summarized using the n, mean, SD, minimum,

median, and maximum by cohort, treatment and overall, on Exploratory Population. %CFB will be presented only for two decimal places.

A by-patient disease activity data elements (numbers of SJC and TJC, PGA, EGA, CRP, ESR, pain VAS and HAQ-DI) scores will be listed based on Exploratory population

American College of Rheumatology

ACR CRP Response Criteria: A Patient is considered as ACR 20 (50/70) responder if

- At least 20%(50% / 70%) improvement in SJC(28 Joint count) compared to baseline, AND
- At least 20%(50% / 70%) improvement in TJC(28 Joint count) compared to baseline, AND
- At least 20%(50% / 70%) improvement in 3 out of following five measures
    1. Patient's assessment of pain on VAS(0-10)
    2. Patient's global assessment (PGA or Patient global score) of the disease (0-10)
    3. Evaluator global assessment (EGA or provider global score) of the disease (0-10)
    4. Patient's assessment of disability on HAQ
    5. Acute phase reactant (C-reactive Protein (CRP))

ACR ESR Response Criteria: A Patient is considered as ACR 20 (50/70) responder if

- At least 20% (50% / 70%) improvement in SJC(28 Joint count) compared to baseline, AND
- At least 20% (50% / 70%) improvement in TJC(28 Joint count) compared to baseline, AND
- At least 20%(50% / 70%) improvement in 3 out of following five measures
    1. Patient's assessment of pain on VAS(0-10)
    2. Patient's global assessment (PGA or Patient global score) of the disease (0-10)
    3. Evaluator global assessment (EGA or provider global score) of the disease (0-10)
    4. Patient's assessment of disability on HAQ
    5. Acute phase reactant (Erythrocyte sedimentation rate (ESR))

ACR 20/50/70 (ESR and CRP) will be summarized using count and percentage of responders by cohort and treatment on Exploratory Population. The percentages of ACR20, (50, or 70) responders are calculated by the equation, "number of ACR20 (50, or 70) responders / number of subjects on each cohort x 100 (%)" by each cohort.

A by-patient listing of percentage of responders of ACR 20/50/70 (ESR and CRP) will be presented on Exploratory Population

Health Assessment Questionnaire - Disability Index (HAQ-DI)

The HAQ-DI consists of eight categories of functioning expressed through 20 questions. Activities are organized under the categories of Dressing & Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, and Activities. Each item is scored on a 4-point scale from 0 to 3, representing Without ANY Difficulty [0], With SOME Difficulty [1], With MUCH difficulty [2], and UNABLE to do [3].

Scoring for the eight functional categories and overall disability index scoring will be performed as follows:
There are eight categories including 20 items; first score within each category:

- Dressing and Grooming, includes 2 items
- Arising, includes 2 items
- Eating, includes 3 items
- Walking, includes 2 items
- Hygiene, includes 3 items
- Reach, includes 2 items
- Grip, includes 3 items
- Activities, includes 3 items

The score for each category will be the single response within the category with the highest score (greatest difficulty).
For example, in the "Eating" category, there are two answers (one for each item). If " Use chopsticks by yourself" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if any "aids or devices" and/or "help from another person" items at the bottom of each page are checked with the exception of “other”, the category to which they apply will be adjusted upward to "2". If the basic score is already "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can only change a category's score to "2"; they do not change the score to a "1" or a "3". Companion aids/devices items for HAQ-DI categories are presented in Table 4-3. No score will be adjusted, if only other is ticked, regardless of the specification.
The score for the disability index will be the mean of the eight category scores. If more than two of the categories, or 25%, are missing, scale will not be scored. If fewer than 2 of the categories are missing, divide the sum of the categories by the number of answered categories. The higher score indicates greater disability.

Table 4-3 Companion aids/devices items for HAQ-DI categories

HAQ-DI	Companion Item

Dressing & Grooming	Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
Arising	Special or built up Chair
Eating	Built up or special utensils
Walking	Cane, Walker, Crutches, Wheelchair
Hygiene	Raised toilet seat, Bathtub seat , Bathtub bar, Long-handled appliances in bathroom
Reach	Long-handled appliances for reach
Grip	Jar opener (for jars previously opened)

Disease activity score 28 (DAS28)

- DAS28 ESR
  - $0.56\times\sqrt{(TJC)}+0.28\times\sqrt{(SJC)}+0.7\times LN(ESR)+0.14^{*}\times(PGA)$
- DAS28 CRP
  - $0.56\times\sqrt{(TJC)}+0.28\times\sqrt{(SJC)}+0.36\times LN((CRP)+1)+0.14^{*}\times(PGA)+0.96$

*Because PGA data in this study are collected with 0-10 scale, instead of 0-100 scale, this coefficient is 0.14, not 0.014 usually found in the formula. LN means log natural.

Clinical disease activity index (CDAI)

- CDAI = SJC + TJC +PGA + EGA

Simplified disease activity index (SDAI)

- SDAI = SJC + TJC +PGA + EGA + 0.1*CRP

Baseline (Day 1), Current value (Day 7), CFB (Day 1 - Day 7) and %CFB ((Day 1 – Day7)/Day1*100) of DAS28 ESR, DAS28CRP, CDAI, and SDAI will be summarized using the n, mean, SD, minimum, median, and maximum by cohort, treatment and overall, on Exploratory Population. %CFB will be presented only for two decimal places.

If any of the elements are missing, then the corresponding parameter will be considered as missing.

A by-patient disease activity data parameters (DAS28 ESR, DAS28CRP, CDAI, and SDAI) scores will be listed based on Exploratory population.

For Exploratory Biomarker refer section 4.15.

4.13.9 Daylight Saving Time (DST)

Not Applicable

4.13.10 Safety Monitoring (Independent Data Monitoring Committee, Data Monitoring Committee, Data and Safety Monitoring Board)

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.

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.

4.14 Cardio Dynamic Analyses

Not Applicable

4.15 Biomarkers

Descriptive statistics for observed values, changes from baseline and % changes from baseline, and a by-patient listing will be provided for the following biomarkers based on Exploratory Population. This data will also be displayed graphically as appropriate.

Biomarker	Description	Read out*
MMP-3	Matrix metalloproteinase-3	
GM-CSF	Granulocyte macrophage colony stimulating factor	
CXCL10	C-X-C motif chemokine ligand 10	
CCL2	C-C motif chemokine ligand 2	
COMP	Cartilage oligomeric matrix protein	
TNF-α	Tumor necrosis factor - α	
TNF-RI	Tumor necrosis factor-RI	
IL-6	Interleukin-6	

* Biomarker name exactly as it will appear in the dataset

Handling of LLOQ and ULOQ

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two limits: Lower limit of quantification (LLOQ) and Upper limit of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

To ensure that biomarkers only have numerical values, censored values will be imputed as follows

- Values below the LLOQ are replaced by LLOQ/2.
- Values above the ULOQ are replaced by ULOQ.

Imputed values are used for summary statistics, inferential analyses and plots (with a special symbol). Values below LLOQ and values above ULOQ are shown as such in the listings. In the

summary table, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.
If the proportion of imputed data is more than 20% for any treatment group at any time point, a footnote is added to the summary statistics table stating that the proportion of values outside the limits of quantification is more than 20% for some treatment groups at some time points and that in such cases summary statistics may be heavily biased.

If the proportion of imputed data for a given biomarker, across all treatment groups and time points, is more than 50%, no summary statistics will be provided, and the data are only listed.

4.16 Adjustments for Covariates

Not Applicable

4.17 Handling of Dropouts or Missing Data

No imputation of missing data will be performed except for partial dates imputation mention in Section 6.2.

4.18 Subgroup Analysis

Not Applicable

4.19 Planned Interim Analyses

Not Applicable

4.20 Determination of Sample Size

No formal sample size calculations were performed. Thirty-two patients were chosen based on feasibility and are considered sufficient to meet the study objectives of this exploratory study.

4.21 Changes in the Conduct of the Study or Planned Analysis

Exploratory population definition is more elaborately defined as per study need.

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[2] Phoenix®WinNonlin® Software Version 8.3. https://www.certara.com

[3] CDAI: Clinical Disease Activity Index for RA (CDAI) (medscape.com)

[4] SDAI: Simplified Disease Activity Index for RA (SDAI) (medscape.com)

[5] DAS28 ESR: https://www.4s-dawn.com/DAS28/

[6] DAS28 CRP : https://www.4s-dawn.com/DAS28/

6 APPENDICES

6.1 Schedule of Assessments

Table 6-1 Schedule of Assessments

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				
Urine pregnancy test (females)	X	X					X	X
FSH (post-menopausal females)	X							
Physical examination[3]	X	X				X	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	
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 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.

6.2 Imputation Rules for Partial Dates

Imputed dates and time will NOT be presented in the listings.

Table 6-2 and Table 6-3 present algorithm for imputing partial dates for TEAE and prior/concomitant medication respectively.

Table 6-2 Algorithm for Treatment-Emergent Adverse Events:

Start/Increase Severity Date	Stop Date	Action
Known	Known	Considered as a treatment-emergent adverse event (TEAE) if start date on or after the date of the first dose of investigational product (IP)
	Partial	Considered as a TEAE if start date on or after the date of the first dose of IP. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as a TEAE if start date on or after the date of the first dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Known	Considered as TEAE, if stop date is after first IP taken date. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date Considered as not TEAE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	Considered as TEAE if stop date is on or after the date of the first dose of IP.
	Partial	The last day of the month and the last month (ie,

Start/Increase Severity Date	Stop Date	Action
		December) will be used if the stop day/month is missing. If the imputed stop date is on or after the first dose of IP considered as a TEAE; if the year is missing, considered as a TEAE
	Missing	Considered as a TEAE

Table 6-3 Algorithm for Prior/Concomitant Medications Categorization:

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	If stop date is prior to the date for the first dose of IP, considered as prior; If stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Missing	Considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
Missing	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if he imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.

6.3 Laboratory Test Parameters

Category	Lab Parameter
Clinical Chemistry	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Blood urea nitrogen (BUN)
	Calcium
	Chloride
	Total cholesterol
	Creatinine
	Creatine kinase (CK)
	Follicle stimulating hormone (FSH) (Screening Visit only; Post-menopausal females only)
	Gamma glutamyl transferase (GGT)
	Glucose
	Lactate dehydrogenase (LDH)
	Phosphorus
	Potassium
	Sodium
	Total bilirubin
	Total protein
	Triglycerides
	C- reactive protein (CRP)
Hematology	White blood cell (WBC) count
	Red blood cell (RBC) count
	Hemoglobin (Hb)
	Hematocrit (HCT)
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	Reticulocytes (count and percentage)
	Neutrophils (percentage and absolute count)
	Lymphocytes (percentage and absolute count)
	Monocytes (percentage and absolute count)
	Eosinophils (percentage and absolute count)
	Basophils (percentage and absolute count)
	Platelet count
	RBC distribution width
Coagulation	Prothrombin time
	Activated partial thromboplastin time (aPTT)
	International Normalized Ratio (INR)
Urinalysis	Bilirubin
	Glucose
	Ketones

	Leukocytes
	Nitrite
	Microscopic (only for abnormal urine stick test findings)-Hyaline casts, cellular casts, granular casts, RBC and WBC
	Blood
	pH and specific gravity
	Protein
	Urobilinogen
	Color and appearance
	Urinary creatinine (to exclude dilution effect)
Viral Serology	Hepatitis B core antibody (anti-HBc)
	Anti-hepatitis B surface antigen (HBsAg)
	Hepatitis C virus antibody (anti-HCV)
	Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies
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
	Barbiturates
	Benzodiazepines
	Oxycodone
	Tricyclic Antidepressants
	Cannabinoids
	Alcohol/Ethanol (to be tested using breathalyzer)
	Cocaine
	Opiates
	Phencyclidine
	3,4-methylenedioxymethamphetamine (MDMA)
	Propoxyphene
	Cotinine
Pregnancy Testing	Urine human beta chorionic gonadotrophin

6.4 ECG Notable Criteria

ECG Parameters	**Definition/threshold**
	New value <= 450 msec
QT, QTcF	New value of > 450 msec and ≤ 480 msec
	New value of > 480 msec and ≤ 500 msec
	New value of > 500 msec
	Increase from baseline <= 30 msec
	Increase from baseline of > 30 msec to ≤ 60 msec
	Increase from baseline of > 60 msec

QTcF = QT corrected using Fridericia's formula

[redacted]

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