STATISTICAL ANALYSIS PLAN

CBR-KA34-3001

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATION STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF KA34 ADMINISTERED VIA INTRA-ARTICULAR INJECTION IN SUBJECTS WITH OSTEOARTHRITIS OF THE KNEE

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - AUTHORS

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE - APPROVAL

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	15MAY2020	PPD	Not Applicable – First Version

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) data for Protocol CBR-KA34-3001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol Amendment 4, dated 02 April 2020.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

- To assess the safety and tolerability of KA34 when administered via intra-articular injection to the knee joint

2.1.1. PRIMARY ENDPOINTS

- Incidence, relatedness, severity, and duration of treatment emergent adverse events (TEAEs)

2.2. SECONDARY OBJECTIVES

- To identify any dose limiting toxicity and determine the maximum tolerated dose of KA34
- To determine pharmacokinetic properties of KA34 in plasma

2.2.1. SECONDARY ENDPOINTS

- Changes from baseline in clinical laboratory test results, vital signs, or electrocardiogram (ECG) results
- Clinically significant findings on physical examination
- Pharmacokinetic parameters of KA34 in plasma including:
  - Maximum observed plasma concentration (C_{max})
  - Dose-adjusted C_{max} (C_{max}/dose)
  - Time to maximum observed plasma concentration (T_{max})

- Area under the plasma concentration vs. time curve from time zero to the last quantifiable concentration (AUC_{0-t})
- Dose-adjusted AUC_{0-t} (AUC_{0-t}/dose)
- AUC from time zero to infinity (AUC_{0-inf})
- Dose-adjusted AUC_{0-inf} (AUC_{0-inf} /dose)
- Terminal elimination rate constant (λz)
- Terminal half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Volume of distribution (Vz/F)

2.3. EXPLORATORY OBJECTIVES

- To assess changes in cartilage and osteoarthritis (OA) symptoms after administration of KA34
- To collect and bank biospecimen samples for exploratory biomarker research

2.3.1. EXPLORATORY ENDPOINTS

- Serum levels of the N-propeptide of type IIA collagen (PIIANP) as a pharmacodynamic marker of collagen synthesis
- Urinary excretion of C-terminal cross-linking telopeptide of type II collagen (CTX-II) as a pharmacodynamic marker of collagen degradation
- Change from baseline in Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the index knee
- Change from baseline of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Version 3.1 total score and the WOMAC pain and function subscale scores
- Utilize banked biospecimen samples for exploratory research related to drug response in OA

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of KA34 when administered via intra-articular injection to

subjects with osteoarthritis of the knee. All subjects will receive a 5 mL injection of KA34 or placebo in the affected knee.

The study will consist of approximately 7 cohorts of subjects who will be randomized to receive KA34 or placebo. KA34 will be provided as a solution with a concentration of 200 µg per mL.

KA34 will be administered as a single dose to the following cohorts:

COHORT	DOSE	N PER COHORT
1	50 µg per knee	4 (3 – Active & 1 Placebo)
2	100 µg per knee	4 (3 – Active & 1 Placebo)
3	200 µg per knee	8 (6 – Active & 2 Placebo)
4	400 µg per knee	8 (6 – Active & 2 Placebo)

The decision to escalate to the next dose cohort will be made by the sponsor, based on the recommendation of the Data Safety Monitoring Board (DSMB), following a (blinded) review of all available safety information from Day 8 post-dose of the preceding dose cohort.

Once the safety and tolerability of single doses of KA34 have been assessed, multiple-dose administration of KA34 will be evaluated. The multiple-dose portion of the study will be initiated after a thorough review of the Day 29 safety data from the single-dose cohorts. During the multiple dose portion of the study, KA34 will be administered as 4 weekly doses to the following cohorts:

COHORT	DOSE	N PER COHORT
5	100 µg per knee per injection	12 (9 – Active & 3 Placebo)
6	200 µg per knee per injection	12 (9 – Active & 3 Placebo)
7	400 µg per knee per injection	12 (9 – Active & 3 Placebo)

The doses administered to subsequent cohorts in either the single or multiple dose portions of the study may be lowered if any safety or tolerability issues are identified which suggest that the planned doses may pose a risk to study participants. Additional dose groups may be added to the study depending on the observed safety and tolerability profile of KA34 or if the pharmacokinetic data permit a higher than anticipated dose while remaining within a safe exposure limit based on the toxicokinetics and safety profile from the nonclinical toxicology studies.

The study will be conducted at approximately 4 sites in the United States. Approximately 60 subjects will be randomized to participate in this trial.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in 'SCHEDULE OF ACTIVITIES' section of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no meaningful changes in the analysis plans relative to the study protocol.

4. PLANNED ANALYSES

4.1. DATA SAFETY MONITORING BOARD (DSMB)

The decision to escalate to the next dose cohort (single or multiple dose escalation) of the study will be made by the sponsor, based on the recommendation of the DSMB following a (blinded) review of all available safety information from Day 8 post-dose of the preceding dose cohort. The safety information considered during this review will include adverse events, changes in vital sign measurements, clinical laboratory test values, and ECG results. Reporting for the DSMB is to be handled by the data management team and is outside the scope of this document.

4.2. INTERIM ANALYSIS

There are no formal interim analyses planned for this study.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics and Pharmacokinetics team following sponsor authorization of this Statistical Analysis Plan, database lock and unblinding of treatment.

5. ANALYSIS SETS

5.1. ALL SUBJECTS RANDOMIZED SET

The all subjects randomized set will contain all subjects who were randomized to the study treatment.

5.2. SAFETY ANALYSIS SET

The safety analysis set will contain all subjects who receive at least one dose of study medication and will be analyzed according to treatment received. Subjects in this population will be used for all safety,

dosing and demographic summaries.

5.3. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic analysis set will consist of all subjects who receive KA34 and have at least 1 measured concentration at a scheduled PK time point after start of dosing without protocol violations or events with potential to affect the pharmacokinetic concentrations. Subjects in this population will be used for all PK parameter analyses.

5.4. PHARMACODYNAMIC ANALYSIS SET

The pharmacodynamic analysis set will consist of all subjects who receive KA34 or placebo (placebo dosed subjects will be pooled and summarized separately) and have at least 1 measured PD value at a scheduled time point after start of dosing without protocol violations or events with potential to affect the PD concentrations. Subjects in this population will be used for all PD analyses/summaries.

6. GENERAL CONSIDERATIONS

Derivation of the PK parameters for KA34 in plasma will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK, PD, and safety summaries, figures and data listings as well as the statistical analysis of the PK and PD variables will be the responsibility of the study biostatistician at IQVIA.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables of safety and PD data will be summarized using descriptive statistics, including N, mean, standard deviation (SD), arithmetic coefficient of variation (CV%) as appropriate, median, minimum, and maximum values. Geometric mean and geometric CV% will be included for PK parameter summaries. CV% will not be presented for change from baseline results.

Results will be summarized if n is greater than or equal to 2 per group and otherwise reported as N/A (ie, Not Applicable).

6.2. TREATMENT SUMMARIZATION

For Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) parts, data will be presented for each dose levels (presented as KA34-XX µg), with placebo subjects from all dose levels combined into a single, overall placebo group (presented as Placebo). Data for all study subjects combined will also be presented when appropriate.

6.3. PRECISION

Safety variables (ie, clinical laboratory values, vital signs, and ECG intervals), including derivations thereof, will be reported to the same precision as the source data.

All PK concentrations and PD results will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK and PD parameters will be rounded for reporting purposes in by-subject listings. The unrounded derived PK and PD parameter data will be considered for the calculation of descriptive statistics and the statistical analysis. For most derived PK and PD parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (eg, T_{max}) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the mean, standard deviation, standard error of the mean, and confidence intervals (where appropriate) will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. Coefficient of determination (R^2) will be reported to 4 decimal places.

6.4. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:
  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.5. BASELINE

Baseline, is defined as the last scheduled non-missing measurement taken prior to the first dose.

6.6. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements will not be included in summary statistics, but will contribute to the assessment of clinical outliers. Early termination results will be recorded as such, and included with the end-of-study summaries.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e. the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

6.7. COMMON CALCULATIONS

For quantitative measurements, change and percent change (as appropriate) from baseline will be calculated as:

- Change from baseline = Post baseline Value – baseline Value, if baseline is not missing.
- Percent change from baseline = 100*[(Post baseline Value – baseline Value)/baseline Value], if baseline if not missing.

6.8. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries and listings will be generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Pharmacokinetic parameters will be derived using noncompartmental methods with the validated computer program Phoenix® WinNonlin® 8.0 or higher (Certara, L.P., Princeton, New Jersey, USA). Graphics will be prepared using the same versions of SAS.

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

Missing safety data will not be imputed.

Missing PK concentrations will be handled as described in Section 15.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The table, listing, and figure shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics and Pharmacokinetics/Pharmacodynamics Early Clinical Development.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. For the SAD and MAD part, subject disposition will be tabulated for each dose levels and for all subjects overall with the number (%) of subjects who are randomly assigned to treatment, complete the study, prematurely discontinue, and the reason for early discontinuation. This summary will be provided for All Subjects Randomized Set. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each subject.

Listings of inclusion/exclusion criteria responses, study eligibility, treatment randomization, and study treatment administration will be provided for the SAD and MAD part.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual subject demographics, contraception review, urine drug screen data, Visual Analogue Scale (VAS) scores, Tibial-femoral radiographs status, magnetic resonance imaging (MRI), follicle-stimulating hormone [FSH] data and banked biospecimen collection details will be presented in listings for the SAD and MAD study part.

Demographic characteristics such as age, sex, race, ethnicity, height, weight, body mass index (BMI), affected knee location and grade of osteoarthritis will be summarized for the SAD and MAD part and tabulated by dose levels and for all subjects overall using the safety analysis set.

Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and

percentages will be presented for sex, race, ethnicity affected knee location and grade of osteoarthritis. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Age (years) = Integer value of [(Date of informed consent – date of birth + 1)/365.25]

11. PROTOCOL DEVIATIONS

11.1. DEVIATIONS RELATED TO STUDY CONDUCT

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedure requirements. The noncompliance may be either on the part of the subject, the site Principal Investigator (PI), or the study site staff. Any subject enrolled who does not meet eligibility criteria will be considered an enrollment deviation. Protocol deviations will be listed including a classification of minor or major, as determined by clinical staff.

11.2. DEVIATIONS RELATED TO PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Changes to the procedures or events, which may impact the quality of the PK or PD data, will be considered significant protocol deviations and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK or PD variables. Examples include, but may not be limited to, incomplete dose delivered, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK or PD sampling. In the case of a significant protocol deviation or event, PK or PD data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

12. MEDICAL HISTORY

Medical History is collected and coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 and will be presented for the safety analysis set.

Medical history will be listed and summarized by system organ class (SOC) and preferred term (PT) for each dose level and all subjects overall for the SAD and MAD study part.

13. MEDICATIONS

Medication usage is collected and coded using the World Health Organization (WHO) Drug Dictionary Version 01Mar2018 and will be presented for the safety analysis set.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.

- 'Concomitant' medications are medications which were taken during the treatment period, or specifically:

  - Started after the first dose of study medication or
  - Started prior to the first dose of study medication and were continued after the first dose of study medication.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

A subject listing of all prior and concomitant medications will be presented.

Concomitant medications will be summarized by preferred term for the SAD and MAD part by dose levels and all subjects overall.

14. STUDY MEDICATION EXPOSURE

Study medication administration data will be listed for the SAD and MAD part.

15. PHARMACOKINETIC ANALYSIS

For SAD and MAD parts, PK data will be listed for each dose levels with placebo subjects from all dose levels combined into a single, overall placebo group (presented as Placebo). Summaries will be

presented by Part (SAD or MAD) and by dose (SAD and MAD combined) for PK evaluations.

15.1. PLASMA CONCENTRATION DATA

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided for both single ascending and multiple ascending doses.

Pre-dose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration.

Pharmacokinetic concentrations which are erroneous due to a protocol deviation (Section 11.2 and as defined in the study protocol), documented handling error or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing a statistical analysis. In this case, the rationale for exclusion must be provided in the Clinical Study Report (CSR). Any other PK concentrations that appear implausible to the Pharmacokineticist/PKPD Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

Plasma concentrations will be summarized using descriptive statistics for each active treatment by dose. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. Lower limit of quantitation for KA34 will be identified in the bioanalytical data of plasma concentrations. Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result, or result not valid) will be reported and displayed generally as “N.R.”. Samples that are collected outside the specified time windows will be included in the PK analysis (actual collection time is used in the parameter analysis) but excluded from the concentration summaries. The PK sampling collection schedule is presented in the Table below.

For the MAD part of the protocol, trough samples will be listed and summarized by dose. Steady-state assessment will be assessed by visual inspection of the mean trough concentration vs time plots (linear scale if concentrations are present). It is expected that the parent drug will not be present in plasma in a quantifiable concentration after 4 hours postdose.

A subject listing of all concentration-time data for each dose levels will be presented. Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented by dose levels on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

SAD: Day 1 PK Sampling Schedule

COLLECTION TIME	ALLOWABLE WINDOW
Pre-Dose	Within 2 hours prior to IP administration

15 Minutes Post-Dose	+/- 2 Minutes
30 Minutes Post-Dose	+/- 3 Minutes
60 Minutes Post-Dose	+/- 5 Minutes
90 Minutes Post-Dose	+/- 5 Minutes
2 hours Post-Dose	+/- 5 Minutes
4 hours Post-Dose	+/- 5 Minutes

MAD: PK Sampling Schedule

Day	COLLECTION TIME	ALLOWABLE WINDOW
1	Pre-Dose	Within 2 hours prior to IP administration
	15 Minutes Post-Dose	+/- 2 Minutes
	30 Minutes Post-Dose	+/- 3 Minutes
	60 Minutes Post-Dose	+/- 5 Minutes
	90 Minutes Post-Dose	+/- 5 Minutes
	2 hours Post-Dose	+/- 5 Minutes
	4 hours Post-Dose	+/- 5 Minutes
8-29	Pre-Dose	+/- 1 Day

15.2. PHARMACOKINETIC PARAMETERS

For PK parameter calculations, both single ascending and multiple ascending dose groups will be summarized by dose as all PK parameters are on Day 1. Predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the

collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

The following PK parameters will be estimated for KA34 in plasma by non-compartmental methods using actual elapsed time from dosing. Day 1 PK parameters will be derived for both SAD and MAD doses. A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters:

C_{max}	Maximum concentration in the sampled matrix (ng/mL), obtained directly from the observed concentration versus time data.
C_{max}/dose	Dose adjusted C_{max} (ng/mL/ug)
T_{max}	Time of maximum concentration (h), obtained directly from the observed concentration versus time data.
AUC_{0-t}	Area under the concentration-time curve in the sampled matrix from zero (predose) to time of last quantifiable concentration (ng·h/mL), calculated by linear up/log down trapezoidal summation.
AUC_{0-t}/dose	Dose adjusted AUC_{0-t}
AUC_{0-inf}	Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to infinite time (ng·h/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{0-t} + C_{last}/\lambda_z$.
AUC_{0-inf}/dose	Dose adjusted AUC_{0-inf} (ng·h/mL/ug)
λ_z	Apparent terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
$t_{1/2}$	Apparent terminal half-life (h), determined as $\ln 2/\lambda_z$.
CL/F	Apparent systemic clearance after extravascular dosing (L/h), calculated as dose divided by AUC_{0-inf}.
Vz/F	Apparent volume of distribution following extravascular dosing (L), calculated as dose divided by $[\lambda_z \cdot AUC_{0-inf}]$

The following PK parameters will be calculated for diagnostic purposes and listed but will not be summarized.

$t_{1/2}$, Interval	The time interval (h) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
Rsq	Goodness of fit statistic for calculation of λ_z (Regression coefficient).
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{0\text{-}inf}\times 100]$. If the $\%AUC_{ex}$ is greater than 20.0% of $AUC_{0\text{-}inf}$, then $AUC_{0\text{-}inf}$ will be listed but not included in summary and inferential statistics.

Pharmacokinetic parameters will be summarized by dose levels using descriptive statistics. Geometric mean will not be calculated for T_{max}; n, minimum, median and maximum will be presented. A subject listing of individual PK parameters for each dose levels will be provided.

A data listing identifying subjects with the following criteria will also be provided to identify subjects with $\%AUC_{ex}$ >20.0%, and Rsq <0.800.

Vertical point plots of individual and geometric mean for primary dose normalized PK parameters (C_{max}/dose, $AUC_{0\text{-}t}$/dose, and $AUC_{0\text{-}inf}$/dose) versus dose will be presented. Additional, graphical presentations of PK data may be added at the discretion of the PK scientist, if further illustration of the PK results is deemed appropriate.

Primary PK variables include $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. All other parameters are secondary variables.

The dose proportionality of the primary PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} summarized by dose delivered, will be assessed statistically using the following power model;

log (parameter) = a + b * log (dose)

where ‘a’ is the intercept and ‘b’ is the slope.

The Day 1 data from both SAD and MAD part may be combined as appropriate for the power model analysis. The intercept ‘a’ and the slope ‘b’ together with 90% confidence intervals will be estimated and presented for each PK parameter. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality with the power model. Dose proportionality analysis will not be performed for the secondary PK parameters.

16. PHARMACODYNAMIC ANALYSIS

16.1. PHARMACODYNAMIC ASSESSMENTS

The pharmacodynamics of KA34 will be evaluated by examining several exploratory endpoints, including biomarker data from serum levels of the N-propeptide of type IIA collagen (PIIANP) and urinary excretion of C-terminal cross-linking telopeptide of type II collagen (CTX-II).

Clinical symptoms as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Version 3.1 total score and the WOMAC pain and function subscale scores, and Tibial-femoral radiographs imaging data are exploratory, see Section 18.

The pre-treatment values for PIIANP and CTX-II endpoints will be compared to post-treatment measurements and both the absolute and percent change from baseline will be summarized. Descriptive statistics for PD endpoints by time point and by dose levels. An exploratory analysis of PK/PD endpoints may also be performed but is not planned.

A listing of PD sample collection times and subject listings of all PIIANP and CTX-II concentration-time data for each dose levels will be presented. Summary tables for both the observed values and the baseline-corrected values. Figures of mean baseline-corrected concentration-time data will be presented by each dose levels. Individual observed concentration-time data for each subject will be presented graphically.

16.2. PHARMACODYNAMIC PARAMETERS

Not applicable to this study.

16.3. PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

Not applicable to this study.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the dose levels for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 21.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of study medication.

Pretreatment AEs are defined as AEs occurring prior to dosing. These events will be presented in the listings only and are not included in the tabular summary of AEs.

See APPENDIX 2 for handling of partial dates for AEs. In the rare case where it is not possible to assess treatment emergence, the AE will be classified as treatment emergent (i.e. the worst case).

Severity

AE Severity is classified as mild/moderate/severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

Relationship to Study Medication

Relationship to study medication, as indicated by the Investigator, is classified as “not related”, “unlikely related”, “possibly related”, or “related”. A “related” TEAE is defined as a TEAE with a relationship to study medication as “possibly related” or “related” to study medication. TEAEs with a missing relationship to study medication will be regarded as “related” to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed for the SAD and MAD study part by dose levels and for all active treated subjects overall, and will include the number and percentage of subjects. Incidence of TEAEs will be tabulated by the following:

- Overall summary for TEAEs displaying number (percent) of subjects with at least one TEAE, with at least one related TEAE, with at least one severe TEAE, with at least one severe related TEAE, with at least one serious AE, with TEAEs leading to discontinuation and with TEAEs leading to death
- Summary of TEAEs by SOC and PT
- Summary of Treatment-related AEs by SOC and PT
- Summary of TEAEs by SOC, PT and Severity
- Summary of Treatment-related AEs by SOC, PT and Severity
- Summary of Serious TEAEs by SOC, PT and Severity

17.1.1. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the variable pertaining to action taken field on the Adverse Events page of the electronic case report form ((e)CRF), and listed.

17.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF, and will be listed.

17.1.3. CTC Grading for Adverse Events

AEs will be graded by the clinics using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 grading system. A summary table will be presented for TEAEs with CTCAE grade >=3 by SOC and PT.

17.2. Deaths

If any subjects die during the study as recorded on the adverse events page of the (e)CRF, the information will be presented in a data listing.

17.3. Laboratory Evaluations

Laboratory results will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Section 7.1.1. Presentations will use SI Units, as provided by the labs.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics for the SAD and MAD parts. Clinical laboratory data collected during study conduct, which were not required per protocol, such as for special testing to evaluate an AE, will be listed separately and not summarized.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual, change from baseline and percentage change from baseline by dose levels and visit (for quantitative measurements)

- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements) for all on-treatment assessments.
- Listing of lab results outside the normal range

17.3.1. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be listed.

17.4. ECG EVALUATIONS

Results of the ECG assessments will be included in the reporting of this study.

Overall interpretation of ECG will be summarized for the following categories:

- Normal
- Abnormal, Not Clinically Significant (ANCS)
- Abnormal, Clinically Significant (ACS)

Number and percent of subjects for each category will be presented by dose levels and schedule assessment visit/day.

The following summary will be provided for 12-lead ECG parameters PQ interval (PR), RR interval (RR), QRS interval (QRS), QT interval (QT), QTc interval (QTcF) and Heart Rate (HR) based on the Safety Population.

- Actual and change from baseline by dose levels and scheduled assessment visit/day for SAD and MAD study part

All ECG assessments will be listed for each study part.

17.5. VITAL SIGNS

The following Vital Signs measurements will be reported for SAD and MAD study part of this study:

- Systolic and Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (^{o}C)

For each study part, the following summaries will be provided for vital signs data based on the Safety Population:

- Descriptive statistics summary for observed and change from baseline by dose levels, scheduled assessment visit/day and timepoint as appropriate

All vital signs data will be listed for each study part.

17.6. PHYSICAL EXAMINATION

Physical exam results will be listed including specification of any abnormalities observed for each study part.

18. EXPLORATORY ANALYSIS

18.1. WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX (WOMAC)

The WOMAC is a validated, patient self-report measure that assesses the dimensions of pain, stiffness and physical function in patients with OA of the hip or knee. In this study the WOMAC will use the 100 mm visual analogue scale (VAS) format.

The WOMAC consists of 24 items divided into 3 subscales:

- Pain (5 items): while walking, using stairs, in bed, sitting or lying, and standing
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): stair use (descending and ascending), rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on socks, taking off

socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, light household duties

The patient's response to each question produces a score that is then summed to derive an aggregated score for each subscale. The total WOMAC score (WOMAC index) provides a measure of overall disability.

Actual and change from baseline of the WOMAC total score and the WOMAC pain and function subscale scores will be presented by dose levels and visit for SAD and MAD study part.

WOMAC scores will be listed for SAD and MAD study part.

18.2. WHOLE-ORGAN MAGNETIC RESONANCE IMAGING SCORE (WORMS)

WORMS is a semi-quantitative scoring method for multi-feature, whole organ evaluation of the knee in OA using conventional MR images. A trained evaluator will review the MRIs and determine a Whole-Organ Magnetic Resonance Imaging Score (WORMS). This will be assessed at Screening visit for SAD part and Screening, Day 90 and Day 180 visits for MAD part of the study.

Actual and Change from baseline in Total Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the index knee will be presented by dose levels and visit for MAD study part.

WORMS will be listed for SAD and MAD study part. Scores by category, scores by joint regions and total scores will be listed for each subject.

19. DATA NOT SUMMARIZED OR PRESENTED

The other domains not summarized or presented are:

- Comments

These domains will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

20. REFERENCES

Smith BP, et al. Confidence Interval Assessment of Dose Proportionality. Pharm Res. 2000;17:10.

Appendix IV of the Guideline on the Investigation on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1): Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1