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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

Investigational Product Number:	KA34
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PROTOCOL APPROVAL

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

Protocol Version: Amendment 4 – 02 APRIL, 2020

PPD

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Date

PPD Arthritis Research

The Scripps Research Institute, La Jolla, CA

DOCUMENT HISTORY

Section Changed	Change	Reason
PROTOCOL SUMMARY Inclusion Criterion #1	Added d. Have undergone a documented bilateral tubal ligation	To add another criterion for female subjects to be considered of non-childbearing potential
PROTOCOL SUMMARY Exclusion Criterion #13	Added NOTE: Subjects who are on aspirin up to 1 gm/day will be eligible for enrollment	To clarify what anti-coagulants are permitted
Multiple Dose Cohort Schedule of Assessments	Changed the Day180 window visit from ±7 days to ±30 days Added Footnote N: Assessments that do not require a visit such as review of concomitant medications for Day180 may be done remotely via phone call, text message, email. PE can be conducted by telemedicine. Laboratory assessment can be done at laboratories other the clinical sites.	To extend visit window for subjects and to allow flexibility to comply with local, state, federal policies due to Covid-19 pandemic for subjects' well being
4 SUBJECT ELIGIBILITY CRITERIA Section 4.1 Inclusion criterion #1	Added d. Have undergone a documented bilateral tubal ligation	To add another criterion for female subjects to be considered of non-childbearing potential
4. SUBJECT ELIGIBILITY CRITERIA 4.2 Exclusion criterion #13	Added NOTE: Subjects who are on aspirin up to 1 gm/day will be eligible for enrollment	To clarify what anti-coagulants are permitted
6 STUDY PROCEDURES 6.3.9 Day 180	Added (In addition to extending the visit window, certain tasks of the Day 180 visit may be conducted by phone, text message, or email for the well-being and safety of the subject related to Covid-19)	To provide flexibility to sites and subjects to comply with local, state, and federal policies due to Covid-19
7 ASSESSMENTS 7.1.5 Electrocardiogram	Added The QT interval will be corrected to QT_C-F (Fridericia); QTcF will be recorded in the eCRF.	To clarify what QTc parameter needs to be entered

Section Changed	Change	Reason
	QTc-F can be corrected with the following equation: $QTcF = \frac{QT}{\sqrt[3]{RR}}$	by sites into the EDC
8. ADVERSE EVENT REPORTING 8.3. Severity Assessment	Added The AEs may also be graded with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.	To clarify how AEs may be graded in addition to mild, moderate, severe

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PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

Osteoarthritis (OA) is a highly prevalent degenerative joint disease that primarily involves the articular cartilage and subchondral bone in addition to the surrounding tissues (Litwic, et al., 2013). OA is characterized by the progressive degeneration of articular cartilage, in part due to the abnormal activation, differentiation, and death of articular chondrocytes, the primary cell type prevalent in cartilage (Goldring & Goldring, 2010). OA is the most common joint disorder in the United States, affecting at least 27 million Americans (Zhang & Jordan, 2010). The joints most often affected by OA are the hands, knees, hips, and spine. The primary symptoms of OA are joint pain, stiffness, and movement limitations. OA may have a profound effect on quality of life, impacting both physical function and psychological well-being of patients.

Current treatment options for OA include pharmacological and non-pharmacological interventions focused primarily on reducing pain and improving physical function. Surgical intervention to replace the hip, knee, or shoulder joint is required for an increasing number of patients who do not have adequate pain relief or preservation of function following more conservative treatment options. There are no approved disease modifying treatments that delay or prevent OA progression or joint destruction (Hunter, 2011).

Since the hallmark of OA is cartilage loss leading to joint destruction, a potential approach to treating OA is stimulation of chondrocyte regeneration from endogenous mesenchymal stem/progenitor cells in the cartilage. KA34 is an experimental compound that exhibits chondrogenic activities both in cell culture and in OA animal models.

This Phase 1 trial will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple intra-articular (IA) injections of KA34 in patients with OA of the knee.

OBJECTIVES AND ENDPOINTS

Primary Objective

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

Primary Endpoint

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

Secondary Objectives

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

Secondary Endpoints

- Changes from baseline in clinical laboratory test results, vital signs, or electrocardiogram (ECG) results
- Clinically significant findings on physical examinations
- 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 ($AUC_{0-\infty}$)
  - Dose-adjusted $AUC_{0-\infty}$ ($AUC_{0-\infty}$/dose)
  - Terminal elimination rate constant (λ_z)
  - Terminal half-life ($t_{½}$)
  - Apparent clearance (CL/F)
  - Volume of distribution (Vz/F)

Exploratory Objectives

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

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

STUDY DESIGN

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:

DOSE	N PER COHORT
50 µg per knee	4 (3 – Active & 1 Placebo)
100 µg per knee	4 (3 – Active & 1 Placebo)
200 µg per knee	8 (6 – Active & 2 Placebo)
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. (see section 9.7, DSMB)

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:

DOSE	N PER COHORT
100 µg per knee per injection	12 (9 – Active & 3 Placebo)
200 µg per knee per injection	12 (9 – Active & 3 Placebo)
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.

STUDY POPULATION

Inclusion Criteria

1. Males willing to use an acceptable method of contraception and females of non-childbearing potential, age 40 to 75 years (inclusive)

   NOTE:

   Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use barrier contraception (male

condom) during the Treatment Period and for at least 7 days after the last dose of KA34. Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

Female subjects must satisfy one of the following criteria to be considered of non-childbearing potential:

a. *Achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum follicle-stimulating hormone (FSH) level consistent with a postmenopausal state*
b. *Have undergone a documented hysterectomy and/or bilateral oophorectomy*
c. *Have medically confirmed ovarian failure*
d. *Have undergone a documented bilateral tubal ligation*

2. Diagnosis of localized osteoarthritis (OA) of the knee by American College of Rheumatology (ACR) clinical and radiographic criteria

   NOTE: Radiographs to confirm the OA diagnosis must be acquired within 6 months (26 weeks) prior to Screening

3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study
4. Subject is willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures
5. Patients with a VAS score of ≥ 40 mm on a 100 mm scale on the index knee determined by the Investigator at Screening

Exclusion Criteria

1. Body Mass Index (BMI) ≥ 40
2. Grade 0, 3 or 4 on the Kellgren and Lawrence classification system as confirmed by tibial-femoral radiographs of the affected knee

   NOTE: Radiographs to confirm the Kellgren and Lawrence Grade must be acquired within 6 months (26 weeks) prior to Screening

3. Previous injury or surgery to the index knee or other joint within 12 months of Screening
4. Any clinically significant laboratory abnormality at Screening
5. Receipt of any investigational product or any experimental therapeutic procedure within the 12 weeks prior to Screening
6. Intra-articular treatment with steroids, hyaluronic acid derivatives, Platelet-Rich Plasma (PRP) or other prolotherapy within the 12 weeks prior to Screening
7. History of previous articular surgery (e.g., partial knee replacement, traumatic meniscus tear, anterior cruciate ligament tear or traumatic cartilage defects) involving the index knee

NOTE: Arthroscopic debridement, meniscectomy, and tendon/ligament repair are permitted as long as the last procedure was at least 12 months prior to Screening

8. History of joint infection, gout, or pseudogout involving the index knee
9. Planned major surgery during study conduct
10. Lesions at the planned injection site that would present a contraindication to local injection of the study drug (e.g., open wounds, psoriatic lesions, or infections of the skin)
11. Use of electrotherapy or acupuncture for OA of the index knee within 28 days of Screening
12. Any known active infection
13. Subjects with a need for anticoagulant treatment for atrial fibrillation or other disorders. NOTE: Subjects who are on aspirin up to 1 gm/day will be eligible for enrollment
14. History of sarcoma or other active malignancy within five years, except adequately treated basal cell and squamous cell carcinoma of the skin
15. Known or suspected infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C
16. History of inflammatory arthritis (such as rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus) and chronic pain syndromes (such as fibromyalgia syndrome or chronic fatigue syndrome)
17. A positive urine drug test at Screening or evidence of current alcohol or substance abuse
18. Any serious, significant medical or psychiatric condition that could compromise subject safety, increase the risk associated with study participation or investigational product administration, or that, in the judgment of the investigator, would make the subject inappropriate for entry into the study
19. Subjects who are site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or employees of the Sponsor or designated representative directly involved in the conduct of the study

STUDY TREATMENTS

- KA34 administered via ultrasound-guided intra-articular injection
- Placebo administered via ultrasound-guided intra-articular injection

STATISTICAL METHODS

This is a Phase 1 study with a primary objective of assessing the safety and tolerability of KA34. The pharmacokinetics and pharmacodynamics of KA34 will be evaluated as secondary and exploratory endpoints. The proposed size of each dose cohort was chosen to provide sufficient information to allow assessment of the safety and tolerability of KA34 and

identify any potential safety signals or dose limiting toxicity before proceeding with administration of higher doses.

Safety and tolerability will be evaluated by summarizing treatment emergent adverse events (TEAEs), serious adverse events, clinical laboratory test results, vital sign measurements, and electrocardiogram (ECG) findings. No formal statistical tests will be conducted to assess the safety or tolerability of KA34.

All PK samples will be analyzed by LC-MS/MS using a validated, sensitive, specific method. Descriptive statistics for plasma concentrations by time point and by treatment group will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (% CV), geometric mean, median, geometric % CV, minimum, and maximum.

Using non-compartmental methods, the plasma concentration versus time data will be used to derive the following PK parameters: C_{max}, C_{max}/dose, T_{max}, AUC_{0-t}, AUC_{0-t}/dose $AUC_{0-\infty}$, $AUC_{0-\infty}$/dose, λ_z, terminal $t_{½}$, CL/F, and V_z/F. Descriptive statistics for PK parameters by treatment group will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), geometric mean, median, geometric %CV, minimum, and maximum. Dose proportionality will be explored.

The pharmacodynamics (PD) of KA34 will be evaluated by examining several exploratory endpoints, including PIIANP, CTX-II, pain and physical functioning as assessed by the WOMAC, and MR imaging data. The pre-treatment values for these 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 treatment group will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), median, minimum, and maximum. An exploratory analysis of PK/PD endpoints may also be performed.

SCHEDULE OF ACTIVITIES

The schedule of activities provides an overview of the protocol visits and procedures. Refer to the appropriate sections of the protocol for detailed information on each procedure. The investigator may schedule an unplanned visit at any time during the study in order to conduct evaluations or assessments required to protect the well-being of the subject.

SINGLE ASCENDING DOSE COHORT SCHEDULE OF ASSESSMENTS												
VISIT NAME	**SCREENING**	**DAY 1[K]**								**DAY 2[A]**	**DAY 8**	**DAY 29[A]**
VISIT NUMBER	**1[I]**	**2**								**3**	**4**	**5**
TIME POST DOSE	NA	PRE DOSE[J]	0	15 MIN	30 MIN	60 MIN	90 MIN	2 HRS	4 HRS			
ALLOWABLE WINDOW	-28 to -1 days			+/- 2 Min	+/- 3 Min	+/- 5 Min	+/- 5 Min	+/- 5 Min	+/- 5 Min		+/- 1 Day	+ 3 Days
Informed Consent	X											
Demography	X											
Medical History	X											
Prior & Concomitant Treatments	X	X							X	X	X	X
Physical Examination	X	X									X	
Height	X											
Weight	X	X									X	
Vital Signs[B]	X	X		X	X	X	X	X	X		X	
12-Lead ECG	X	X									X	
Tibial-Femoral Radiographs[C]	X											
Safety Laboratory Tests[D]	X	X									X	
Follicle Stimulating Hormone Test[E]	X											
Urine Drug Screen[D]	X											
MRI	X											
Eligibility Review	X	X										
Randomization		X										
VAS	X											
WOMAC[F]		X									X	
PK Blood Sample		X		X	X	X	X	X	X			
PIIANP Blood Sample		X									X	
CTX-II Urine Sample		X									X	
Banked Biospecimen Sample - Serum[G]		X							X		X	
Banked Biospecimen Sample – Synovial Fluid[G]		X										
IP Administration			X									
Adverse Events[H]			X	X	X	X	X	X	X	X	X	X

SINGLE ASCENDING DOSE COHORT SCHEDULE OF ASSESSMENTS												
VISIT NAME	**SCREENING**	**DAY 1[K]**								**DAY 2[A]**	**DAY 8**	**DAY 29[A]**
VISIT NUMBER	**1[I]**	**2**								**3**	**4**	**5**
TIME POST DOSE	NA	PRE DOSE[J]	0	15 MIN	30 MIN	60 MIN	90 MIN	2 HRS	4 HRS			
Contraception Review	X								X	X	X	X

A Day 2 and Day 29 Visits may be conducted via telephone.

B Vital signs collection includes temperature, seated blood pressure, and pulse rate

C Tibial-femoral x-rays to confirm the diagnosis of OA and the Kellgren & Lawrence Grade must be of acceptable quality and acquired within 6 months prior to Screening

D Safety laboratory testing includes hematology, chemistry, and urinalysis; will be performed at the site's laboratory

E For female subjects; will be performed at the site's laboratory

F The WOMAC should be administered at the beginning of the visit prior to completing other procedures

G Optional banked biospecimen collection

H Adverse Events are captured starting at time of consent. Any Adverse Events during Screening and Day 1 will be captured and noted as part of medical history

I Screening procedures may be completed across multiple days during the 28 day screening period and do not need to be conducted on consecutive days

J All D1 predose laboratory assessments should be conducted within 48 hours prior to IP administration and other pre-dose assessments conducted within 2 hours prior to IP administration

K Subjects may be discharged after at least 2 hours of safety observation following the last procedure

MULTIPLE ASCENDING DOSE COHORT SCHEDULE OF ASSESSMENTS																	
VISIT NAME	**SCREENING**	**DAY 1[K]**								**DAY 2[A]**	**DAY 8[K]**	**DAY 15[K]**	**DAY 22[K]**	**DAY 29**	**DAY 50[A]**	**DAY 90[M]**	**DAY 180[M, N]**
VISIT NUMBER	**1[I]**	**2**								**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
TIME POST FIRST DOSE	NA	PRE-DOSE[J]	0	15 MIN	30 MIN	60 MIN	90 MIN	2 HRS	4 HRS								
ALLOWABLE VISIT WINDOW	-28 to -1 days			+/- 2 Min	+/- 3 Min	+/- 5 Min	+/- 5 Min	+/- 5 Min	+/- 5 Min		+/- 1 Day[L]	+/- 1 Day[L]	+/- 1 Day[L]	+/- 1 Day	+ 3 Days	+/- 7 Days	+/- 30 Days
Informed Consent	X																
Demography	X																
Medical History	X																
Prior & Concomitant Treatments	X	X							X	X	X	X	X	X	X	X	X
Physical Examination	X	X									X			X		X	X
Height	X																
Weight	X	X									X	X	X	X		X	X
Vital Signs[B]	X	X		X	X	X	X	X	X		X	X	X	X		X	X
12-Lead ECG	X	X									X			X		X	X
Tibial-Femoral Radiographs[C]	X																
Safety Laboratory Tests[D]	X	X									X			X		X	X
Follicle Stimulating Hormone Test[E]	X																
Urine Drug Screen[D]	X																
MRI	X															X	X
Eligibility Review	X	X															
Randomization		X															
VAS	X																
WOMAC[F]		X									X			X		X	X
PK Blood Sample		X		X	X	X	X	X	X		X	X	X	X			
PIIANP Blood Sample		X									X	X	X	X		X	X
CTX-II Urine Sample		X									X	X	X	X		X	X
Banked Biospecimen Sample-Serum[G]		X							X		X	X	X	X			
Banked Biospecimen Sample-Synovial Fluid[G]		X									X	X	X				
IP Administration			X								X	X	X				

MULTIPLE ASCENDING DOSE COHORT SCHEDULE OF ASSESSMENTS																	
VISIT NAME	**SCREENING**	**DAY 1[K]**								**DAY 2[A]**	**DAY 8[K]**	**DAY 15[K]**	**DAY 22[K]**	**DAY 29**	**DAY 50[A]**	**DAY 90[M]**	**DAY 180[M, N]**
VISIT NUMBER	**1[I]**	**2**								**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
TIME POST FIRST DOSE	NA	PRE-DOSE[J]	0	15 MIN	30 MIN	60 MIN	90 MIN	2 HRS	4 HRS								
ALLOWABLE VISIT WINDOW	-28 to -1 days			+/- 2 Min	+/- 3 Min	+/- 5 Min	+/- 5 Min	+/- 5 Min	+/- 5 Min		+/- 1 Day[L]	+/- 1 Day[L]	+/- 1 Day[L]	+/- 1 Day	+ 3 Days	+/- 7 Days	+/- 30 Days
Adverse Events [H]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Review	X								X	X	X	X	X	X			

A Day 2 and Day 50 Visits may be conducted via telephone

B Vital signs (temperature, seated blood pressure, and pulse rate) should be collected pre-dose and 30 minutes after dosing on Days 8, 15, and 22

C Tibial-femoral x-rays to confirm the diagnosis of OA and Kellgren & Lawrence Grade must be of acceptable quality and acquired within 6 months prior to Screening

D Safety laboratory testing includes hematology, chemistry, and urinalysis; will be performed at the site's laboratory

E For female subjects; will be performed at the site's laboratory

F The WOMAC should be administered at the beginning of the visit prior to completing other procedures

G Optional banked biospecimen collection

H Adverse Events are captured starting at time of consent. Any Adverse Events during Screening and Day 1 will be captured and noted as part of medical history

I Screening procedures may be completed across multiple days during the 28 day screening period and do not need to be conducted on consecutive days

J All D1 predose laboratory assessments should be conducted within 48 hours prior to IP administration and other pre-dose assessments conducted within 2 hours prior to IP administration

K Subjects may be discharged after at least 2 hours of safety observation following the last procedure

L There should be minimum of 7 days between the IA injections

M Procedures may be split into 2 days to allow for the completion of multiple procedures

N Assessments that do not require a visit such as review of concomitant medications for Day180 may be done remotely via phone call, text message, email. PE can be conducted by telemedicine. Laboratory assessment can be done at laboratories other the clinical sites

1. INTRODUCTION

Osteoarthritis (OA) is a highly prevalent, degenerative joint disease that involves the articular cartilage and subchondral bone in addition to the surrounding tissues (Litwic, et al., 2013). OA is characterized by the progressive degeneration of articular cartilage, in part due to abnormal activation, differentiation, and death of articular chondrocytes, the primary cell type present in cartilage (Goldring & Goldring, 2010). OA is the most common joint disorder in the United States, affecting at least 27 million Americans (Zhang & Jordan, 2010). The joints most often affected by OA are the hands, knees, hips, and spine. The primary symptoms of OA are joint pain, stiffness, and movement limitations. OA may have a profound effect on quality of life, impacting both the physical function and psychological well-being of patients.

Current treatment options for OA include pharmacological and non-pharmacological interventions focused primarily on reducing pain and improving physical function. Surgical intervention to replace the hip, knee, or shoulder joint is required for an increasing number of patients who do not have adequate pain relief or preservation of function following more conservative treatment options. There are no approved disease modifying treatments that delay or prevent OA progression or joint destruction (Hunter, 2011).

Since the hallmark of OA is cartilage loss leading to joint destruction, a potential approach to treating OA is stimulation of chondrocyte regeneration from endogenous mesenchymal stem/progenitor cells in the cartilage. KA34 is an experimental compound that exhibits chondrogenic activity both *in vitro* and in animal models of OA.

1.1. Mechanism of Action/Indication

KA34 is a first-in-class, low molecular weight, drug-like molecule which promotes articular cartilage repair and is being explored as a potential treatment for osteoarthritis of the knee.

1.2. Background

Osteoarthritis (OA) is a highly prevalent disease characterized by progressive degeneration of the articular cartilage (Litwic, et al., 2013). The prevalence of symptomatic OA increases with age and BMI. Symptomatic OA of the knee occurs in approximately 10% of men and 13% of women aged 60 years or older in the United States (Zhang & Jordan, 2010).

OA is generally classified as idiopathic, with no identifiable cause, or secondary. Secondary OA is related to a known medical condition or event, such as trauma, congenital or developmental disease, calcium deposition disease, or another bone and joint disorder such as rheumatoid arthritis. Idiopathic OA can impact the hands, feet, knees, hips, spine, or other joints such as the shoulders, ankles, or wrists. Idiopathic OA is considered generalized if it impacts three or more types of joints (Altman, et al., 1986).

OA is diagnosed based on clinical examination, laboratory test results, and radiographic findings. Developing a sensitive, specific classification system for OA is challenging due to the non-specific nature of the symptoms and the lack of a definitive diagnostic test. Radiography can detect changes in articular cartilage and tissue reaction around the joint, but

radiographs are not sufficient to diagnose OA as 40% of patients with radiographic changes consistent with OA do not have clinical symptoms (Altman, et al., 1986).

The widely used American College of Rheumatology (ACR) criteria for knee OA require the presence of knee pain in combination with other signs or symptoms, radiographic changes, or laboratory findings and provide a series of algorithms (decision trees) that support the classification of OA (Altman, et al., 1986). The severity of knee OA is generally graded using the Kellgren and Lawrence radiological classification system (Kellgren & Lawrence, 1957).

1.2.1. Pharmacology and Pharmacokinetics

KA34 was investigated in *in vitro* and *in vivo* pharmacodynamic studies. KA34 effectively induces human mesenchymal stem cell (MSC) differentiation into chondrocytes *in vitro* and improves osteoarthritic outcomes in animal models of OA.

In vitro primary pharmacodynamic studies demonstrated that KA34 can induce a two- to four-fold increase in mRNA expression of the chondrogenic genes sex-determining region Y-Box 9 (SOX9), proteoglycan 4 (PRG4), and cartilage-oligo matrix protein (COMP). KA34 at 1 µM had no off-target inhibition or stimulation higher than 50% in receptor binding, enzyme and uptake assays.

KA34 was investigated in multiple *in vivo* primary pharmacodynamic studies in both rat and dog models of OA. KA34 treatment improved osteoarthritic outcomes in both rat and canine models of OA. Reductions in cartilage degeneration and cartilage depth ratios occurred at doses of 1 µg and 35 µg per knee in rat and dog, respectively, when KA34 was administered IA either once weekly or once every other week. Normalizing these putative efficacious doses by using rat, dog, and human synovial knee volume, the predicted human efficacious dose is approximately 200 µg per knee. KA34 treatment also significantly increased the plasma biomarker PIINP in the dog which is consistent with induction of cartilage regeneration, the hypothesized mechanism of action.

Pharmacokinetic data for KA34 were obtained from specific pharmacokinetic studies and from adjunct toxicokinetic studies included with toxicology evaluations. The overall range of IA doses explored was 2.1 µg – 12 µg per rat knee and 35 µg – 100 µg per dog knee. The overall range of IV doses explored was 0.2 – 2.5 mg/kg in the rat and 0.125-1.25 mg/kg in the dog.

Upon intra-articular injection, KA34 exhibits low plasma levels and rapid clearance in preclinical species. A single IA dose of KA34 at 2.11 µg per rat knee resulted in an $AUC_{0-\tau}$ of 12.1 ng*h/mL and a C_{max} of 13.8 ng/mL. In a five-week rat IV dose study at 2.5 mg/kg/week KA34 (NOAEL), the Study Day 1 average $AUC_{0-\tau}$ was 2915 ng*h/mL and the average C_{max} was 5930 ng/mL. Therefore, the rat IV/IA AUC exposure margin was 240-fold and the C_{max} exposure margin was 429-fold. A similar comparison in dogs given a study day one single IA dose of 35 µg/knee (efficacious dose) versus an IV NOEL dose of 1.25 mg/kg resulted in dog IV/IA AUC exposure margin of 453-fold and the C_{max} exposure margin of 1123-fold.

KA34 had no effects on central and peripheral nervous system activities or measured respiratory parameters. In an IV conscious, telemetered, cardiovascular dog study, a

transient decrease in systolic blood pressure (14 and 15 mmHg) was noted at 0.5 hours after treatment at doses of 0.600 and 1.250 mg/kg, respectively. These minimal blood pressure changes occurred at much higher exposure levels than are anticipated via IA injection. Vital signs, including seated blood pressure, will be monitored before and after dosing in this study.

Additional information about KA34 may be found in the Investigator's Brochure (IB).

1.2.2. Toxicology

A nonclinical toxicology program was conducted to support the administration of KA34 in this first in human clinical trial. The Sprague-Dawley rat and Beagle dog were selected as the relevant nonclinical species due to a similar *in vitro* metabolite profile compared to human.

The KA34 toxicology program consisted of: single dose IA and IV non-GLP toxicity studies in the rat and dog, 5-week IA and IV repeat dose toxicity GLP studies in the rat and dog with a 14-day recovery period, and a battery of *in vitro* and *in vivo* GLP genotoxicity studies.

In the single dose IA (femoro-tibial joint) toxicity studies, KA34 was well tolerated up to 12 µg per rat and 200 µg per dog. In the single dose IV toxicity studies, KA34 was well tolerated up to 2.4 mg/kg in rats and 1.2 mg/kg in dogs.

In the 5-week rat IA toxicity study, the no-observed-effect-level (NOEL) was determined to be 6µg/rat/week. In the 5-week rat IV toxicity study, the no-observed-adverse-effect-level (NOAEL) was determined to be 2.5 mg/kg/week. In the 5-week dog IA toxicity study, the NOEL was determined to be 100 µg/dog/week. In the 5-week dog IV toxicity study, the NOAEL was determined to be 1.25 mg/kg/week.

KA34 was not genotoxic in *in vitro* bacterial mutation and mammalian micronucleus tests or in the *in vivo* rat micronucleus assay.

Additional information about KA34 may be found in the Investigator's Brochure (IB).

1.3. Rationale

1.3.1. Study Rationale

KA34 is being investigated as a potential treatment for patients suffering from OA. Treatments with KA34 improves osteoarthritic outcomes in rat and dog models of OA. KA34 was safe and well tolerated when administered IA and IV in GLP toxicology studies in rats and dogs. This first in human study will evaluate the safety and tolerability of KA34 in subjects with OA of the knee. The study will also allow for pharmacokinetic and pharmocodynamic assessment of KA34 in this patient population to inform future development plans. KA34 will be administered via intra-articular injection to minimize systemic exposure.

1.3.2. Dose Rationale

This selection of doses for this first in human study was based on the relevant preclinical data. The initial cohorts treated in the study will receive single-ascending doses of KA34. Once the safety and tolerability of single doses of KA34 have been established, additional cohorts will receive multiple ascending doses of KA34.

The dog was selected as the most sensitive species based on a lower local safety margin, lower human equivalent dose (HED), and lower systemic exposure compared to the rat. The HED was determined based on the no observed effect level (NOEL) from the 5-week dog IA toxicity study. The 100 µg/knee/week NOEL in dogs was normalized by synovial volume and injected concentrations of KA34 in the knee. The synovial knee volume used in the calculation was 1.2 mL for the dog and 7 mL for human (Kraus, et al., 2007) (Wehr, et al., 2007). The NOEL 100 µg concentration normalized in the dog was 83.3 µg/mL and 583 µg/knee in humans. Based on a 3X safety margin and the lack of any remarkable findings at the high dose from the 5-week IA and IV toxicity studies in dog and rat, the initial clinical maximum recommended starting dose (MRSD) was calculated as 194 µg/knee. However, the KA34 concentration analysis of the 200 µg/mL/week formulation used during Week 5 of the five-week dog IA repeat toxicity study was found to be below the nominal concentration, up to -26% of nominal in dogs. Therefore, a modified MRSD of 143 µg/knee (74% of the 194 µg/knee) was calculated.

The starting dose in humans selected for the single ascending dose portion of the study is 50 µg, approximately 1/3 of the MRSD and 1/12 of the NOEL. The starting dose selected for the multiple ascending dose portion of the study is 100 µg, which is approximately 1/6 of the NOEL.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

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

2.2. Primary Endpoints

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

2.3. Secondary Objectives

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

2.4. 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 ($AUC_{0-\infty}$)
- Dose-adjusted $AUC_{0-\infty}$ ($AUC_{0-\infty}$/dose)
- Terminal elimination rate constant (λ_z)
- Terminal half-life ($t_{½}$)
- Apparent clearance (CL/F)
- Volume of distribution (Vz/F)

2.5. Exploratory Objectives

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

2.6. 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, function, and stiffness scores
- Utilize banked biospecimen samples for exploratory research related to drug response in OA

3. STUDY DESIGN

3.1. Study Overview

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:

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

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 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:

DOSE	N PER COHORT
100 µg per knee per injection	12 (9 – Active & 3 Placebo)
200 µg per knee per injection	12 (9 – Active & 3 Placebo)
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. Dose Escalation

The decision to escalate to the next dose cohort of the study 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 in the single dose portion of the study(see Section 9.7, DSMB) The decision to initiate the multiple dose portion of the study will be made by the sponsor, after all cohorts have completed dosing in the single ascending dose portion of the study and based on the recommendation by the DSMB following a (blinded) review of all available safety information from Day 29.

The decision to escalate to the next dose cohort in the multiple dose portion of the study will be made by the sponsor based on the recommendation of the DSMB following a (blinded) review of the available safety data from Day 8 post-dose, after all subjects have been dosed in 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. Dose escalation will be stopped if it is determined that the limits of safety or tolerability have been reached; this decision will be made following the recommendation by the DSMB.

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.

Dose escalation will be paused if any of the following occur:

- 50% or more of the subjects at a given dose level develop similar clinically significant laboratory, ECG, or vital sign abnormalities or severe adverse events (AEs) in the same organ class, indicating dose-limiting intolerance
- A serious adverse event (SAE) that is deemed causally related to KA34 by the DSMB
- Additional safety data from a dose cohort are required to determine whether the limit of safety or tolerability has been reached
- Any other safety findings that, at the discretion of the DSMB, indicate that dose escalation should be halted

If dose escalation is halted, dosing may resume if the DSMB and sponsor determine that there is no unacceptable risk to subjects after a thorough review of the available safety information. The study may be terminated or the protocol may be amended if dosing cannot be resumed without adequate measures to ensure subject safety.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Males willing to use an acceptable method of contraception and females of non-childbearing potential, age 40 to 75 years (inclusive)

   NOTE:

   Male patients with a female spouse/partner of childbearing potential or a pregnant or breastfeeding spouse or partner must agree to use barrier contraception (male condom) during the Treatment Period and for at least 7 days after the last dose of KA34. Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy.

   Female subjects must satisfy one of the following criteria to be considered of non-childbearing potential:

   a. *Achieved postmenopausal status defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause <u>and</u> a serum follicle-stimulating hormone (FSH) level consistent with a postmenopausal state*
   b. *Have undergone a documented hysterectomy and/or bilateral oophorectomy*
   c. *Have medically confirmed ovarian failure*

d. Have undergone a documented bilateral tubal ligation

2. Diagnosis of localized osteoarthritis (OA) of the knee by American College of Rheumatology (ACR) clinical and radiographic criteria

   NOTE: Radiographs to confirm the OA diagnosis must be acquired within 6 months prior to Screening

3. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study
4. Subject is willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures
5. Patients with a VAS score of ≥ 40 mm on a 100 mm scale on the index knee determined by the Investigator at Screening

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Body Mass Index (BMI) ≥ 40
2. Grade 0, 3 or 4 on the Kellgren and Lawrence classification system as confirmed by tibial-femoral radiographs of the affected knee

   NOTE: Radiographs to confirm the Kellgren and Lawrence Grade must be acquired within 6 months prior to Screening

3. Previous injury or surgery to the index knee or other joint within 12 months of Screening
4. Any clinically significant laboratory abnormality at Screening
5. Receipt of any investigational product or any experimental therapeutic procedure within the 12 weeks prior to Screening
6. Intra-articular treatment with steroids, hyaluronic acid derivatives, Platelet-Rich Plasma (PRP) or other prolotherapy within the 12 weeks prior to Screening
7. History of previous articular surgery (e.g., partial knee replacement, traumatic meniscus tear, anterior cruciate ligament tear or traumatic cartilage defects) involving the index knee.

   NOTE: Arthroscopic debridement, meniscectomy, and tendon/ligament repair are permitted as long as the last procedure was at least 12 months prior to Screening

8. History of joint infection, gout, or pseudogout involving the index knee
9. Planned major surgery during study conduct
10. Lesions at the planned injection site that would present a contraindication to local injection of the study drug (e.g., open wounds, psoriatic lesions or infections of the skin)

11. Use of electrotherapy or acupuncture for OA within 28 days of Screening
12. Any known active infection
13. Subjects with a need for anticoagulant treatment for atrial fibrillation or other disorders.
    NOTE: Subjects who are on aspirin up to 1 gm/day will be eligible for enrollment
14. History of sarcoma or other active malignancy within five years, except adequately treated basal cell and squamous cell carcinoma of the skin
15. Known or suspected infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C
16. History of inflammatory arthritis (such as rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus) and chronic pain syndromes (such as fibromyalgia syndrome or chronic fatigue syndrome)
17. A positive urine drug test at Screening or evidence of current alcohol or substance abuse
18. Any serious, significant medical or psychiatric condition that could compromise subject safety, increase the risk associated with study participation or investigational product administration, or that, in the judgment of the investigator, would make the subject inappropriate for entry into the study
19. Subjects who are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or employees of the Sponsor or designated representative directly involved in the conduct of the study

4.3. Randomization Criteria

Subjects will be randomized into the study once they have completed screening and have satisfied all eligibility criteria. Subjects will be randomized in a 3:1 ratio to receive KA34 or placebo in each dose cohort.

4.4. Contraception Requirements

All fertile male subjects who are sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 7 days after the last dose of investigational product. The investigator or his or her designee will confirm that the subject has selected an appropriate method of contraception from the permitted list of highly effective contraception methods below and will confirm that the subject has been instructed in its consistent and correct use.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly and include the following:

- Established use of hormonal methods of contraception associated with inhibition of ovulation (e.g., oral, inserted, injected, implanted, or transdermal)

- Correctly placed copper-containing intrauterine device (IUD)
- Male condom or female condom used in combination with a separate spermicide product (i.e., foam, gel, film, cream, or suppository)
- Male sterilization with absence of sperm in the post-vasectomy ejaculate
- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label)

At each study visit during the active treatment period and for 7 days after the last dose of investigational product, the investigator or designee will remind fertile, male subjects of the need to use highly effective contraception consistently and correctly and document the conversation in the subject's source documentation. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject's partner.

Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse, obviates the need for contraception as long as the subject affirms that he remains abstinent during the active treatment period and for 7 days after the last dose of study medication.

4.5. Designated Qualified Medical Personnel

The contact information for the Medical Monitor is provided in the study contact list located in the Study Manual.

5. STUDY TREATMENTS

For this study, the investigational product is KA34 or matching placebo. KA34 or placebo will be administered at the following dose levels to the single dose cohorts:

- 50 µg per IA injection
- 100 µg per IA injection
- 200 µg per IA injection
- 400 µg per IA injection

KA34 or placebo will be administered once a week for 4 weeks at the following dose levels to the multiple dose cohorts:

- 100 µg per IA injection
- 200 µg per IA injection
- 400 µg per IA injection

KA34 will be supplied by the Sponsor in amber glass vials as a sterile solution with a concentration of 200 µg per mL. Matching placebo will be provided in identical vials. Each vial will contain 5 mL of KA34 or placebo. The vials will be packaged in boxes for shipment to investigative sites.

The investigational product (IP) labels will include the protocol number, the contents, the lot number, storage conditions, and an investigational use caution statement.

KA34 should not be administered after the use-by date provided by the Sponsor.

5.1. Investigational Product Storage

Site pharmacy staff must ensure that all investigational product (IP) is stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product vials should be stored in their original containers and in accordance with the labels. The vials of KA34 and matching placebo should be stored in a freezer at a temperature of -15º- -25º Celsius.

See the Pharmacy Manual for more detailed information on IP storage conditions and dilution instructions.

The site must be capable of measuring and documenting the daily minimum and maximum temperatures for all freezers used to store IP. Temperature monitoring information should be captured from the time of IP receipt throughout the duration of the study. A site procedure that ensures active evaluation for temperature excursions should be in place and appropriate documentation of temperature monitoring must be available. The minimum and maximum temperature should be checked each business day to confirm that no excursion occurred and the site should have the capability to view the minimum/maximum temperature for all non-working days upon return to normal operations. The temperature monitoring device and freezer used to store IP should be regularly inspected to ensure they are maintained in working order.

Any excursions from the labeled storage conditions should be reported to the Sponsor's designated representative upon discovery. In the event of an excursion, the site should ensure the product is returned to the storage conditions described in the labeling as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor's designated representative.

Once a temperature excursion is identified, the investigational product must be quarantined and cannot be administered until the Sponsor's designated representative provides permission to use the investigational product. Specific details for the reporting and management of temperature excursions will be provided in the Pharmacy Manual.

Receipt of investigational product, opening and closing the freezer, and other routine handling operations where the IP is briefly out of the temperature range described in the labeling will not be considered excursions.

5.2. Allocation to Treatment

The investigator or a designee will assign subject identification numbers to the subjects as they are screened for the study. The Sponsor's designated representative will provide a randomization schedule and eligible subjects will be randomized to receive the study

treatment regimen assigned to the corresponding randomization number. Subjects may be randomized once all screening procedures have been completed and eligibility has been confirmed. Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system. Details regarding randomization procedures will be provided in the IRT Manual.

5.3. Preparation and Dispensing

KA34 and placebo will be prepared by a pharmacist or other qualified pharmacy personnel at the site. The pharmacy staff who prepare KA34 or placebo will be unblinded. The investigational product will be dispensed and administered in blinded fashion to ensure that the investigator, non-pharmacy site personnel, and the subject remain blinded.

The KA34 and placebo vials must be thawed prior to preparation. The vials of KA34 and placebo are for single use only. The Pharmacy Manual will provide detailed instructions on how to prepare the investigational product for administration.

5.4. Administration

KA34 or placebo will be administered via ultrasound-guided intra-articular injection in accordance with the standard of care procedures at the site. KA34 or placebo should be administered by the Principal Investigator or another qualified physician trained in accepted techniques for delivering agents to the knee joint. Strict aseptic injection technique must be employed during administration of KA34 or placebo. The physician should use his or her professional judgment to choose the best approach and injection site for the individual subject.

Excess fluid should be aspirated from the knee prior to injection of the investigational product. Ultrasound must be used to guide the procedure. The physician should save the ultrasound images documenting the needle placement until the close-out visit for this study. Each injection will consist of 5 mL of KA34 or placebo.

Subjects should be advised to avoid strenuous activity after receiving KA34 or placebo and to manage pain in accordance with standard post-injection care instructions used at the site. Post injection flare, characterized by localized pain, may occur within several hours of an intra-articular knee joint injection. It usually resolves within 48 hours. Any instances of post injection flare should be reported as an adverse event.

5.5. Investigational Product Accountability

The site must maintain adequate records documenting the receipt, preparation, use, loss, or other disposition of the investigational product. All investigational product will be accounted for using an IP (Investigational Product) accountability form/record.

5.6. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product at the site. The investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special

instructions provided by the Sponsor's designated representative. All IP destruction must be adequately documented.

5.7. Maintaining Study Blinding and Breaking the Blind

The Principal Investigator and other site staff not directly involved in the preparation or dispensing of investigational product will be blinded to study treatment throughout the conduct of the study. Blood specimens will be obtained from all subjects for PK analysis to maintain the study blind at the investigator site. Specimens from subjects randomized to placebo will not be routinely analyzed for PK parameters. A blinded monitor will be assigned for each site who will remain blinded until all monitoring for the study has been completed and the database has been released. Personnel of the Sponsor or designated representative involved in the conduct of the study will remain blinded as to study treatment during the conduct of the study. To minimize the potential for bias, treatment randomization information will be kept confidential and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

At the initiation of the study, the site will be instructed on procedures for breaking the blind for safety reasons. The study blind should be maintained whenever possible to avoid bias. The blind may be broken in circumstances when knowledge of the treatment received by a subject is essential for further medical management of the subject. The blind may also be broken if necessary to determine whether dosing or dose escalation should be paused. When the blind is broken, the reason must be fully documented and entered on the case report form (CRF).

5.8. Concomitant Treatments

Subjects may be on treatment for symptomatic relief of OA, including nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors. The dose of any ongoing OA medications should be held stable during the study if possible.

All concomitant medications taken during the study must be recorded in the source documentation and CRF. The indication, daily dose, start and stop dates of administration should be documented. Any non-drug treatments for OA, such as physical therapy, should also be recorded in the appropriate CRF module. All subjects will be questioned about concomitant treatment at each clinic visit.

Medications taken during Screening will be documented as prior treatments. Medications taken after the first dose of investigational product will be documented as concomitant treatments.

6. STUDY PROCEDURES

6.1. Screening (Visit 1)

Subjects will be screened during the 28 days prior to administration of investigational product (Day 1) to confirm that they meet the entry criteria for the study. The investigator or an appropriate designee will obtain informed consent from each subject prior to conducting any study procedures.

The following procedures will be completed during Screening to determine subject eligibility for participation:

- Obtain written informed consent
- Collect demographic information
- Administer VAS pain scale
- Obtain medical history, including any history of illegal drug, alcohol, and tobacco use. Include a history of the subject's OA symptoms and diagnosis.
- Obtain complete history of all prescription drugs, non-prescription drugs, dietary supplements, and herbal supplements taken within the last 30 days. Obtain a history of all previous and current pharmacological treatments for OA and all non-drug treatments for OA within the previous 12 months.
- Conduct full physical examination
- Obtain height and weight
- Obtain temperature and seated blood pressure (BP) and pulse rate (PR)
- Obtain 12-lead ECG
- Review the subject's tibial-femoral radiographs to confirm the diagnosis of OA and determine the Kellgren-Lawrence Grade. If the subject does not have tibial-femoral radiographs of adequate quality that were acquired within 6 months of the anticipated Day 1 date, new radiographs should be obtained.
- Collect blood and urine samples for the following:
  - Safety laboratory tests (hematology, chemistry, and urinalysis)
  - Serum FSH concentration (for female subjects)
  - Urine drug test
- Obtain MRI according to the procedures outlined in the Imaging Manual
- Review contraception requirements and ensure the subject is willing to comply with the contraception requirements throughout the study (for male subjects)
- Confirm and document that the subject satisfies the eligibility criteria

Screening procedures may be completed across multiple days during the 28-day screening period and do not need to be conducted on consecutive days.

Subjects who are screen failures may be rescreened for study participation if deemed appropriate by the investigator.

6.2. Treatment & Follow-Up Procedures – Single Dose Cohorts

6.2.1. Day 1 (Visit 2)

The following procedures will be completed on Day 1:

- Collect blood and urine samples for safety laboratory tests
- Collect pre-dose PK blood sample
- Collect pre-dose serum sample for PIIANP assessment
- Collect pre-dose urine sample for CTX-II assessment
- Collect pre-dose serum sample for biospecimen banking (if the subject has consented to provide this optional sample)

  NOTE: All D1 pre-dose laboratory assessments should be conducted within 48 hours prior to IP administration and other pre-dose assessments conducted within 2 hours prior to IP administration.
- Administer WOMAC
- Review any changes in the subject's medical history or concomitant medication use since Screening
- Conduct targeted physical examination
- Obtain weight
- Obtain temperature and seated BP and PR
- Obtain 12-lead ECG
- Confirm and document that the subject continues to meet all eligibility criteria
- Randomize the subject

  NOTE: Subjects may be randomized prior to the completion of the Day 1 procedures listed above if necessary to allow pharmacy staff sufficient time to prepare IP.
- Collect pre-dose synovial fluid sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Administer KA34 or placebo
- Obtain temperature and seated BP and PR at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, and 4 hours after dosing
- Collect blood samples for PK analysis at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, and 4 hours after dosing
- Collect serum sample for biospecimen banking at 4 hours post-dosing (if the subject has consented to provide this optional sample)
- Assess adverse events starting at the time of IP administration by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Record any concomitant medications administered while the subject was at the study site
- Remind the subject about study contraception requirements (if applicable)

- Subjects may be discharged after at least 2 hours of safety observation following the last procedure

6.2.2. Day 2 (Visit 3)

The following procedures will be completed on Day 2:

- Record any concomitant medications used by the subject since leaving the site on Day 1
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Remind the subject about study contraception requirements and confirm highly effective contraception is being used (if applicable)

The Day 2 visit may be conducted via telephone. However, the PI may also ask the subject to return to the site on Day 2 and conduct any additional evaluations or assessments required to protect the well-being of the subject.

6.2.3. Day 8 (Visit 4)

The following procedures will be completed on Day 8:

- Administer WOMAC
- Record any changes in concomitant medications
- Conduct full physical examination
- Obtain weight
- Obtain temperature and seated BP and PR
- Obtain 12-lead ECG
- Collect blood and urine samples for safety laboratory tests
- Collect serum sample for PIIANP assessment
- Collect serum sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Collect urine sample for CTX-II assessment
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Remind the subject about study contraception requirements and confirm highly effective contraception was used for 7 days after the last IP administration (if applicable)

6.2.4. Day 29 (Visit 5)

The following procedures will be completed on Day 29, which is the 'End of Study' Visit:

- Record any concomitant medications used by the subject since Day 8

- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Remind the subject about study contraception requirements and confirm highly effective contraception was used for 7 days after the last IP administration (if applicable)

The Day 29 visit may be conducted via telephone. However, the PI may also ask the subject to return to the site on Day 29 and conduct any additional evaluations or assessments required to protect the well-being of the subject.

6.3. Treatment & Follow-Up Procedures – Multiple Dose Cohorts

6.3.1. Day 1 (Visit 2)

The following procedures will be completed on Day 1:

- Collect blood and urine samples for safety laboratory tests
- Collect pre-dose PK blood sample
- Collect pre-dose serum sample for PIIANP assessment
- Collect pre-dose urine sample for CTX-II assessment
- Collect pre-dose serum sample for biospecimen banking (if the subject has consented to provide this optional sample)

  NOTE: All D1 pre-dose laboratory assessments should be conducted within 48 hours prior to IP administration and other pre-dose assessments conducted within 2 hours prior to IP administration.
- Administer WOMAC
- Review any changes in the subject's medical history or concomitant medication use since Screening
- Conduct targeted physical examination
- Obtain weight
- Obtain temperature and seated BP and PR
- Obtain 12-lead ECG
- Confirm and document that the subject continues to meet the eligibility criteria
- Randomize the subject

  NOTE: Subjects may be randomized prior to the completion of the Day 1 procedures listed above if necessary to allow pharmacy staff sufficient time to prepare IP.
- Collect pre-dose synovial fluid sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Administer KA34 or placebo

- Assess temperature and seated BP and PR at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, and 4 hours after dosing
- Collect blood samples for PK analysis at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, and 4 hours after dosing
- Collect serum sample for biospecimen banking at 4 hours post-dosing (if the subject has consented to provide this optional sample)
- Assess adverse events starting at the time of IP administration by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Record any concomitant medications administered while the subject was at the study site
- Remind the subject about study contraception requirements (if applicable)
- Subjects may be discharged after at least 2 hours of safety observation following the last procedure

6.3.2. Day 2 (Visit 3)

The following procedures will be completed on Day 2:

- Record any concomitant medications used by the subject since leaving the site on Day 1
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Remind the subject about study contraception requirements and confirm highly effective contraception is being used (if applicable)

The Day 2 visit may be conducted via telephone. However, the PI may also ask the subject to return to the site on Day 2 and conduct any additional evaluations or assessments required to protect the well-being of the subject.

6.3.3. Day 8 (Visit 4)

The following procedures will be completed on Day 8:

- Collect blood and urine samples for safety laboratory tests
- Collect pre-dose blood sample for PK analysis
- Collect pre-dose serum sample for PIIANP assessment
- Collect pre-dose urine sample for CTX-II assessment
- Collect pre-dose serum sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Administer the WOMAC
- Record any changes in concomitant medications

- Conduct targeted physical examination
- Obtain weight
- Obtain pre-dose temperature and seated BP and PR
- Obtain 12-lead ECG
- Collect pre-dose synovial fluid sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Administer KA34 or placebo
- Obtain temperature and seated BP and PR 30 minutes after dosing (+/- 5 minute window)
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as “How do you feel?”
- Remind the subject about study contraception requirements and confirm highly effective contraception is being used (if applicable)

6.3.4. Day 15 (Visit 5)

The following procedures will be completed on Day 15:

- Collect pre-dose blood sample for PK analysis
- Collect pre-dose serum sample for PIIANP assessment
- Collect pre-dose urine sample for CTX-II assessment
- Collect pre-dose serum sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Record any changes in concomitant medications
- Obtain weight
- Obtain temperature and seated BP and PR
- Collect pre-dose synovial fluid sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Administer KA34 or placebo
- Obtain temperature and seated BP and PR 30 minutes after dosing (+/- 5 minute window)
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as “How do you feel?”
- Remind the subject about study contraception requirements and confirm highly effective contraception is being used (if applicable)
- Subjects may be discharged after at least 2 hours of safety observation following the last procedure

6.3.5. Day 22 (Visit 6)

The following procedures will be completed on Day 22:

- Collect pre-dose blood sample for PK analysis
- Collect pre-dose serum sample for PIIANP assessment
- Collect pre-dose urine sample for CTX-II assessment
- Collect pre-dose serum sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Record any changes in concomitant medications
- Obtain weight
- Obtain temperature and seated BP and PR
- Collect pre-dose synovial fluid sample for biospecimen banking (if the subject has consented to provide this optional sample)
- Administer KA34 or placebo
- Collect temperature and seated BP and PR 30 minutes after dosing (+/- 5 minute window)
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as “How do you feel?”
- Remind the subject about study contraception requirements and confirm highly effective contraception is being used (if applicable)
- Subjects may be discharged after at least 2 hours of safety observation following the last procedure

6.3.6. Day 29 (Visit 7)

The following procedures will be completed on Day 29:

- Administer the WOMAC
- Record any changes in concomitant medications
- Conduct targeted physical examination
- Obtain weight
- Obtain temperature and seated BP and PR
- Obtain12-lead ECG
- Collect blood and urine samples for safety laboratory tests
- Collect blood sample for PK analysis
- Collect serum sample for PIIANP assessment
- Collect serum sample for biospecimen banking (if the subject has consented to provide this optional sample)

- Collect urine sample for CTX-II assessment
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as “How do you feel?”
- Remind the subject about study contraception requirements and confirm highly effective contraception was used for 7 days after the last IP dose (if applicable)

6.3.7. Day 50 (Visit 8)

The following procedures will be completed on Day 50:

- Record any changes in concomitant medications
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as “How do you feel?”

The Day 50 visit may be conducted via telephone. However, the PI may also ask the subject to return to the site on Day 50 and conduct any additional evaluations or assessments required to protect the well-being of the subject.

6.3.8. Day 90 (Visit 9)

The following procedures will be completed on Day 90:

- Administer the WOMAC
- Record any changes in concomitant medications
- Conduct full physical examination
- Obtain weight
- Obtain temperature and seated BP and PR
- Obtain 12-lead ECG
- Collect blood and urine samples for safety laboratory tests
- Collect serum sample for PIIANP assessment
- Collect urine sample for CTX-II assessment
- Obtain MRI according to the procedures outlined in the Imaging Manual
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as “How do you feel?”
- Procedures in Visit 9 may be completed in 2 days if there is a conflict with MRI scheduling.

6.3.9. Day 180 (Visit 10)

(For the well-being and safety of the subject related to Covid-19, in addition to extending the visit window, certain tasks of the Day 180 visit that do not require on site visit may be

conducted by phone, text message or email. Physical exam can be conducted by telemedicine. Laboratory assessment can be done at laboratories other the clinical sites)

The following procedures will be completed on Day 180:

- Administer the WOMAC
- Record any changes in concomitant medications
- Conduct a full physical examination
- Obtain weight
- Obtain temperature and seated BP and PR
- Obtain 12-lead ECG
- Collect blood and urine samples for safety laboratory tests
- Collect serum sample for PIIANP assessment
- Collect urine sample for CTX-II assessment
- Obtain MRI according to the procedures outlined in the Imaging Manual
- Assess adverse events by spontaneous reporting and by asking the subject to respond to a non-leading question such as "How do you feel?"
- Procedures in Visit 10 may be completed in 2 days if there is a conflict with MRI scheduling.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the investigator or the Sponsor for safety reasons or due to the inability to comply with the protocol-required schedule of visits or procedures. Subjects who request to discontinue receipt of study treatment will be discontinued from the study. An early termination visit should be conducted for subjects who receive study drug and then are prematurely withdrawn from the study if at all possible.

The early termination visit will include a physical exam and documentation of weight, vital signs, ECG, and WOMAC score. A review of ongoing AEs, concomitant medications and confirmation of barrier or contraception use for male subjects at least 7 days from the last day of the received dose will be documented. Blood and urine will be collected for safety laboratory tests (hematology, chemistry, and urinalysis), PK, PIIANP, and CTXII analyses.

If a subject decides to withdraw consent, this should be explained in the source documentation. If possible, the investigator should inquire about the reason for withdrawal, request that the subject return for an early termination visit, and follow up with the subject regarding any unresolved AEs for 30 days.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject at least twice. After 2 attempts, site staff may send a registered letter to the subject. If no response is received, the subject will be considered lost to follow-up. All attempts to contact the subject

and information received during contact attempts must be recorded in the source documentation.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who are discontinued from or withdraw from the study may be replaced.

7. ASSESSMENTS

Every effort should be made to ensure that all protocol-required tests and procedures are completed. However, there may be circumstances outside the control of the investigator that make it impossible to comply with the Schedule of Assessments. In such cases, the investigator should take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test is not performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken in the source documentation. The Sponsor's designated representative should be informed of any protocol deviations that impact subject safety within 24 hours of awareness.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed as defined in the Schedule of Activities and Study Procedures section of this protocol at the site local laboratory:

Table 1 Laboratory Tests

Hematology – Complete Blood Count	
• Red Blood Cell (RBC) Count • Hemoglobin (Hb) • Hematocrit (Hct) • Mean Corpuscular Volume (MCV) • Mean Corpuscular Hemoglobin (MCH) • Mean Corpuscular Hemoglobin Concentration (MCHC) • Platelet Count (Plt)	• White Blood Cell (WBC) Count • Absolute Neutrophil Count • Absolute Lymphocyte Count • Absolute Monocyte Count • Absolute Eosinophil Count • Absolute Basophil Count
Chemistry – Metabolic Panel	
• Glucose • Calcium • Albumin • Total Protein • Sodium • Potassium • Bicarbonate (Total CO_2) • Chloride	• Blood Urea Nitrogen (BUN) • Creatinine • Alkaline Phosphatase (ALP) • Alanine Aminotransferase (ALT) • Aspartate Aminotransferase (AST) • Total Bilirubin
Urinalysis	
• Specific Gravity • pH • Protein • Glucose • Ketones • Blood (Hemoglobin) • Leukocyte Esterase	• Nitrite • Bilirubin • Urobilinogen • Microscopic Examination[A]
Other Laboratory Tests	
• Follicle-Stimulating Hormone (FSH)[B] • Urine Drug Screen	

A Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase

B For female subjects

The minimum requirement for urine drug screening includes cocaine, opiates/opioids, benzodiazepines, and amphetamine.

Urine drug screening conducted during Screening in the SAD and MAD part of the study must be negative for subjects to receive investigational product.

Unscheduled clinical laboratory assessments may be obtained at any time during the study to assess potential safety concerns. In any instances where a subject's liver function test results or clinical signs or symptoms suggest that the subject may be experiencing a drug-induced liver injury, the additional tests listed in Table 2 should be conducted and the results should be discussed with the Medical Monitor.

Table 2 Tests for Suspected Cases of Drug-Induced Liver Injury (DILI)

- ALP
- ALT
- AST
- Total Bilirubin
- Direct Bilirubin
- Indirect Bilirubin
- Albumin
- Creatine Kinase (CK)
- Gamma-Glutamyl Transferase (GGT)
- Prothombin Time and International Normalized Ratio (PT /INR)

The Medical Monitor should be notified of any potential cases of drug-induced liver injury within 24 hours of awareness.

7.1.2. Physical Examinations

Physical examinations may be conducted by a physician or another medically-qualified individual such as a physician's assistant or a nurse practitioner. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart, lung, lymph nodes, and the gastrointestinal, musculoskeletal, and neurological systems. The targeted physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

7.1.3. Height and Weight Measurements

Height will be recorded during Screening.

For measuring weight, a scale with appropriate range and resolution should be used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and should remain still during measurement of weight.

7.1.4. Vital Signs

Temperature, blood pressure (BP), and pulse rate (PR) will be measured at times specified in the Schedule of Activities and Study Procedures section of this protocol.

Temperature should be measured orally.

Seated BP should be measured with the subject's feet flat on the floor and back supported and the subject's arm supported at the level of the heart. BP should be recorded to the nearest mm Hg after at least 5 minutes of rest. Subjects should be instructed not to speak during measurements. A properly sized and calibrated BP cuff should be used for each measurement. PR will be measured in the brachial/radial artery for at least 30 seconds. The use of an automated device for measuring BP and PR is acceptable. When the timing of these measurements coincides with a blood collection, BP and PR should be obtained prior to the nominal time of the blood collection with the exception of Screening and Pre-Dose.

On Day 1, vital signs will be measured pre-dose and at 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, and 4 hours after dosing for all subjects (+/- 5 minutes). For subjects in the multiple dose cohorts, vital signs will be measured pre-dose and 30 minutes post-dosing (+/- 5 minute window) on Day 8, Day 15, and Day 22.

7.1.5. Electrocardiograms

12-Lead ECGs should be obtained at times specified in the Schedule of Activities and Study Procedures section of this protocol.

All ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position. The Principle Investigator or a medically qualified designee should review all ECG measurements obtained during the study. All ECG results should be reviewed for any clinically significant findings and consultation with a cardiologist should be obtained if necessary. Post-treatment ECG results should be compared to the Day 1 baseline ECG measurements.

The QT interval will be corrected to QTc-F (Fridericia); QTcF will be recorded in the eCRF.

QTc-F can be corrected with the following equation:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

7.2. Pharmacokinetics

Blood samples to provide plasma for PK analysis will be collected into appropriately labeled tubes containing EDTA or another anticoagulant at the times specified in the Schedule of Activities and Study Procedures sections of the protocol. Detailed collection, processing, storage, and shipment instructions for PK samples will be provided to the investigator site prior to initiation of the study.

All efforts should be made to obtain PK samples at the specified nominal time relative to dosing. The following windows are allowed for collection of the post-dose PK samples on Day 1:

Table 3 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

The exact date and time of collection for each sample should be noted on the source document and in the CRF.

Samples will be analyzed using a validated analytical method in compliance with the bioanalytical laboratory standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (e.g., sample collection and processing, interim storage, or shipping conditions) must be documented and reported to the Sponsor's designated representative. On a case -by -case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, as well as for other exploratory purposes. These data will not be included in the clinical study report (CSR).

7.3. Pharmacodynamic Samples

Serum samples for analysis of PIIANP and urine samples for analysis of CTX-II will be collected as specified in the Schedule of Assessments. Detailed collection, processing, storage, and shipment instructions for these samples will be provided to the investigator site prior to initiation of the study.

Pharmacodynamic (PD) samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (e.g., sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor's designated representative. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

The time of collection for each sample should be noted on the source document and in the CRF.

Samples will be analyzed using a validated analytical method in compliance with the bioanalytical laboratory standard operating procedures (SOPs).

As part of understanding the pharmacodynamics of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

7.3.1. Procollagen Type IIA N-Propeptide (PIIANP)

Type II collagen is the most abundant protein of cartilage matrix and alterations in turnover of this molecule are believed to play a role in the progressive loss of cartilage in OA (Sharif, et al., 2007). Type II procollagen is synthesized in two splice forms, type IIA and type IIB. The N-propeptide of type IIA collagen (PIIANP) can be specifically measured and may represent a biological marker of phenotypic changes of chondrocytes (Rousseau, et al., 2004) (Sharif, et al., 2007). It has been shown that serum levels of type IIA procollagen amino

terminal propeptide (PIIANP) are decreased in patients with knee osteoarthritis (Rousseau, et al., 2004). Serum levels of PIIANP will be collected in this study as analyzed as a potential biomarker for type II collagen synthesis.

7.3.2. C-Terminal Telopeptide of Type II Collagen (CTX-II)

Type II Collagen is the predominant collagen in cartilage and is degraded by proteolytic enzymes secreted by the chondrocyte and synoviocytes. CTX-II peptides, released from the action of these enzymes, are eliminated in urine. Urine CTX-II is thus a biochemical marker of cartilage degradation (Garnero & Delmas, 2003).

7.4. 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 (Bellamy, et al., 1988). The WOMAC is widely used and is available in 5-point Likert, 11-point numerical rating and 100-mm visual analogue scale (VAS) formats. 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.

On visits where the WOMAC is administered, subjects should complete the WOMAC prior to undergoing other study procedures.

7.5. Imaging

7.5.1. Radiographs

Tibial-femoral radiographs that are of acceptable quality should be reviewed by the Principal Investigator or a medically-qualified designee to confirm the diagnosis of OA and the Kellgren and Lawrence Grade. The radiographs must be acquired within 6 months prior to Screening. Details regarding the radiographic procedures will be provided in the Imaging Manual.

7.5.2. Magnetic Resonance Imaging (MRI)

MR images of the index knee will be acquired during Screening for all subjects. Subjects in the multiple-ascending dose cohorts will also have post-treatment MR images collected on Day 90 and Day 180 to support exploratory analyses of structural changes to the knee after

administration of KA34. A trained evaluator will review the MRIs and determine a 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 (Peterfy, et al., 2002). Alternative semi-quantitative scoring methods to grade cartilage pathology with MRI such as the Knee Osteoarthritis Scoring System (KOSS) or the Boston-Leeds Osteoarthritis Knee Score (BLOKS) may also be used. Details of the MRI procedures will be provided in the Imaging Manual.

7.6. Banked Biospecimens

Biospecimen samples will be collected for banking to support exploratory research relating to biomarkers and predictors of drug response in OA if the subject provides written informed consent for the collection of these samples.

- Serum biospecimen samples for exploratory biomarker research will be collected pre- and post-doing and one week after the final IP dose as specified in the Study Procedures and Schedule of Activities sections of the protocol

- Synovial fluid aspirate biospecimen samples for exploratory biomarker research will be collected prior to IP administration on dosing days as specified in the Study Procedures and Schedule of Activities sections of the protocol

Detailed collection, processing, storage, and shipment instructions for the banked biospecimen samples will be provided to the investigator site prior to initiation of the study.

All banked biospecimen samples will be handled in a manner that protects the subject's privacy and confidentiality. Banked biospecimens will labeled with a subject identification number at the site. The data generated from these banked biospecimens will be indexed by this identification number. Biospecimen samples will be kept until destruction in facilities with access limited to authorized personnel and biospecimen-derived data will be stored on password-protected computer systems. Information that links the subject identification number and any personally identifying information (such as the subject's name or address) will be held solely at the study site. Banked biospecimen samples will be used only for the purposes described in the protocol and informed consent document; any other uses would require additional Institutional Review Board or Ethics Committee (IRB/EC) approval.

Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely. A subject may withdraw consent for the use of his or her banked biospecimen samples at any time by making a request to the investigator; upon such a request, any remaining banked biospecimen samples for the subject will be destroyed, but data already generated from biospecimens provided by the subject will continue to be available to protect the integrity of existing analyses.

7.7. Blood Volume

The total blood sampling volume for individual subjects in the single-ascending dose cohorts in this study is approximately 60 mL. The total blood sampling volume for individual subjects in the multiple-ascending dose cohorts in this study is approximately 120 mL.

Additional blood samples may be taken for safety assessments at the PI's discretion. The total volume taken during the study will not exceed 550 mL during any period of 56 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Reporting Requirements and Timeline

Adverse event (AE) information will be collected in this study from the time of first administration of investigation product (Day 1) until 28 calendar days after the last administration of IP (Day 29 for subjects in the single-ascending dose cohorts and Day 180 for subjects in the multiple-ascending dose cohorts). All observed or volunteered treatment emergent adverse events that occur during this timeframe should be recorded in the source documentation and the CRF. If an adverse event is ongoing at the end of the AE collection period, additional follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the Medical Monitor.

Serious adverse events (SAEs) must be reported to the Medical Monitor within 24 hours of awareness, regardless of whether the event is determined by the investigator to be related to the investigational product under study. If an SAE is fatal or life -threatening, notification to the Medical Monitor must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional follow-up-information on previously reported events. In the rare situation that the investigator does not become immediately aware of the occurrence of an SAE, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event. Serious adverse events (SAEs) that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to the Medical Monitor even if they occur after the active AE collection period.

The investigator may be requested by the Medical Monitor to obtain specific follow-up information for SAEs or other AEs of special interest in an expedited fashion. This information may be more detailed than that recorded on the CRF. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Medical Monitor.

As part of ongoing safety reviews conducted by the Medical Monitor, DSMB or Sponsor representatives, any non-serious AE that is determined by the Medical Monitor to be serious will be reported by the Medical Monitor as an SAE. To assist in the determination of seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the SAE report. Detailed instructions for SAE reporting will be provided prior to initiation of enrollment at each site.

8.1.1. Causality Assessment

The investigator's assessment of causality must be provided for all AEs, both serious and non-serious. The investigator must record the causal relationship on the CRF and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the evidence or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented in study records.

In addition, if the investigator determines that an SAE is associated with study related procedures, the investigator must record this causal relationship in the source documents and CRF and report such an assessment in accordance with the SAE reporting requirements.

8.1.2. Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.1.3. Withdrawal from the Study Due to Adverse Events

Withdrawal due to AEs, whether serious or non-serious, should be distinguished from withdrawal due to other causes and recorded on the CRF.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage to be considered an AE. Examples of AEs include, but are not limited to:

- Abnormal test findings
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease
- Drug abuse
- Drug dependency

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose
- Drug withdrawal

- Drug misuse
- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure via breastfeeding
- Medication error
- Occupational exposure

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- The test result is associated with accompanying symptoms
- The test result requires additional diagnostic testing or medical/surgical intervention
- The test result leads to a discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- The test result is considered to be an AE by the DSMB, PI or Medical Monitor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect
- Is considered to be an important medical event

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Same-day surgeries (as outpatient/same-day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for workup of a persistent pretreatment laboratory abnormality)
- Social admission (e.g., subject has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Preplanned treatments or surgical procedures

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function
MODERATE	Interferes to some extent with subject's usual function
SEVERE	Interferes significantly with subject's usual function

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function), but would not be classified as serious unless it met one of the criteria for SAEs listed above.

The AEs may also be graded with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Potential cases of drug-induced liver injury (DILI) are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the liver function test abnormalities.

A potential DILI or Hy's law case is considered a confirmed case after the results of reasonable investigations have been received and an alternative etiology has been excluded.

8.4.2. Exposure during Pregnancy

An exposure during pregnancy (EDP) occurs if a female becomes pregnant either while receiving or having been exposed (e.g., because of treatment or environmental exposure) to the investigational product. An example of environmental exposure would be a case involving direct contact with the Sponsor's product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

If a male has been exposed (e.g., because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy, this is also considered an exposure during pregnancy.

Any instances of exposure during pregnancy that occur during this study should be reported to the Medical Monitor within 24 hours of investigator awareness. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports. The investigator will follow the pregnancy until completion or pregnancy termination and notify the Medical Monitor of the outcome. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a pregnancy termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

The following pregnancy outcomes should also be reported to the Medical Monitor as SAEs:

- Spontaneous abortion (includes miscarriage and missed abortion)
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the Medical Monitor. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with a Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

Detailed instructions for EDP reporting will be provided prior to initiation of enrollment at each site.

8.4.3. Exposure during Breastfeeding

Exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to the Medical Monitor within 24 hours of the investigator's awareness. Detailed instructions for reporting an exposure during breastfeeding will be provided prior to initiation of enrollment at each site.

8.4.4. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) has unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure should be reported to the Medical Monitor within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded

on a CRF; however, a copy of the completed report form should be maintained in the investigator site file.

Detailed instructions for occupational exposure reporting will be provided prior to initiation of enrollment at each site.

8.4.5. Medication Errors

Medication errors may involve the administration or consumption of the investigational product by the wrong subject, at the wrong time, or at the wrong dosage strength. In the event of a medication dosing error, the Medical Monitor should be notified immediately. Medication errors should be recorded in the source documentation and reported in the CRF. If a medication error is associated with a serious adverse event, SAE reporting procedures should be followed.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be provided in a statistical analysis plan (SAP). The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

This is a Phase 1 study with a primary objective of assessing the safety and tolerability of KA34. The size of each dose cohort was chosen to provide sufficient information to allow assessment of the safety and tolerability of KA34 and identify any potential safety signals or dose limiting toxicity before proceeding with administration of higher doses.

9.2. Efficacy Analyses

No efficacy analyses will be conducted for this study.

9.3. Pharmacokinetic Analyses

All PK samples will be analyzed by LC-MS/MS using a validated, sensitive, specific method. Descriptive statistics for plasma concentrations by time point and by treatment group will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), geometric mean, median, geometric %CV, minimum, and maximum.

The individual plasma concentration data for KA34 treated subjects with actual sampling dates and times relative to dosing will be used to derive the PK parameters. Using non-compartmental methods (WinNonlin® 6.3 or higher, Certara, L.P., 1699 S Hanley Road, St Louis MO 63144 USA), the plasma concentration versus time data will be used to derive the following PK parameters: C_{max}, C_{max}/dose, T_{max}, AUC_{0-t}, AUC_{0-t}/dose $AUC_{0-\infty}$, $AUC_{0-\infty}$/dose, λ_z, terminal $t_{½}$, CL/F, and Vz/F. Descriptive statistics for PK parameters by treatment group will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), geometric mean, median, geometric %CV, minimum, and maximum. Dose proportionality will be assessed.

9.4. Pharmacodynamic Analyses

The pharmacodynamics of KA34 will be evaluated by examining several exploratory endpoints, including biomarker data from PIIANP and CTX-II, clinical symptoms as assessed by the WOMAC, and imaging data. The pre-treatment values for these endpoints will be compared to post-treatment measurement and both the absolute and percent change from baseline will be summarized. Descriptive statistics for PD endpoints by time point and by treatment group will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), median, minimum, and maximum. An exploratory analysis of PK/PD endpoints may also be performed.

9.5. Safety Analyses

Safety and tolerability will be evaluated by compiling standard summary statistics for treatment emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory test results, vital sign measurements, and electrocardiogram (ECG) findings. No formal statistical tests will be conducted on the safety or tolerability of KA34.

Changes from baseline for the ECG parameters including QT interval, heart rate, QTc interval, PR interval, and QRS interval will be summarized by treatment and time.

AEs, ECGs, BP, PR, and clinical laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, as appropriate.

9.6. Interim Analysis

No interim analysis will be conducted for this study.

9.7. Data Safety Monitoring Board (DSMB)

This study will use an external data safety monitoring board.

The safety of the study will be monitored by the PI, the Medical Monitor, Sponsor Medical Personnel and the DSMB.

A DSMB will be appointed to provide data and safety oversight. The DSMB will review all SAEs and AESIs as cumulative reports at their scheduled meetings or individually on an ad hoc basis, as needed. All SUSARs will be reviewed on an ad hoc basis. The PI may request that the DSMB review an SAE report on an ad hoc basis, as described in the DSMB charter. The DSMB has the power to recommend holding or stopping of the study to the Sponsor, if deemed necessary following a study intervention-related SAE. The DSMB will review blinded data and recommend to the Sponsor and the investigators whether to continue or terminate the study based on the data review.

The DSMB will consist of three independent clinical experts. Sponsor or Designate will provide general statistical and administrative support to the DSMB. The DSMB will operate under the terms of a charter that will be approved by the DSMB. Communication by the DSMB will be shared with the Sponsor and the investigators. The DSMB will make

recommendations to the sponsor regarding safety issues, trial conduct, and modifying, extending or stopping the trial.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The Medical Monitor and the Sponsor's designated representatives will conduct periodic monitoring visits during the study at all investigative sites to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitor and the Sponsor's designated representatives may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow the Sponsor's designated representatives and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by the sponsor, or companies working with or on behalf of the sponsor, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify the Medical Monitor immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the Sponsor's designated representative to prepare the investigator site for the inspection and will allow the Sponsor's designated representative, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to the Sponsor's designated representative. Before response submission to the regulatory authorities, the investigator will provide the Sponsor's designated representative with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and other relevant site personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required for each included subject. The completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The

CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are accurate. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and should not obscure the original entry.

Data collected on the CRFs must match the source documentation. In most cases the source documents are medical records. However, in some cases the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at the Sponsor's designated representative's site that clearly identifies those data for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or the Sponsor, the investigator agrees to keep accurate records, including the identity of all participating subjects, all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor's designated representative should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another investigator, another institution, or to an independent third party arranged by the Sponsor's designated representative.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain the Sponsor's designated representative's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents such as recruitment advertisements from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to the Sponsor's designated representative.

The only circumstance in which a protocol amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and the Sponsor's designated representative in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The informed consent documents and any subject materials used during the informed consent process must be reviewed and approved by the Sponsor's designated representative, approved by the IRB/EC before use, and available for inspection. Informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to the Sponsor's designated representative and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by the Sponsor or the Sponsor's designated representative in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, the Sponsor and the Sponsor's designated representative will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory authority in any area of the world or if the investigator becomes aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, the Sponsor's designated representative should be informed immediately.

In addition, the investigator will inform the Sponsor's designated representative immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard and of any serious breaches of this protocol or of ICH GCP of which the investigator becomes aware.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, investigational product safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of KA34 at any time.

If a study is prematurely terminated, the Sponsor's designated representative will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy within 7 days. As directed by the Sponsor's designated representative, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by the Sponsor

The Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov and other public registries in accordance with applicable local laws/regulations.

The Sponsor posts clinical trial US Basic Results on www.clinicaltrials.gov for interventional studies that evaluate the safety and/or efficacy of a Sponsor product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

In all cases, study results are reported by the Sponsor in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

15.2. Publications by Investigators

The Sponsor supports the exercise of academic freedom and has no objection to publication by the Principal Investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Sponsor's product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide the Sponsor an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to the Sponsor at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Sponsor product related information necessary to the appropriate scientific presentation or understanding of the study results. In the event that confidential study or Sponsor product related information is necessary for the appropriate scientific presentation or understanding of the study results, the Sponsor and the investigator will use their best efforts to minimize the need to disclose confidential information.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the clinical study agreement (CSA) between the Sponsor and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abs	absolute
ACR	American College of Rheumatology
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration vs time curve
BLOKS	Boston-Leeds Osteoarthritis Knee Score
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
Calibr	California Institute for Biomedical Research
CK	creatine kinase
C_{max}	maximum observed plasma concentration
CO^2	carbon dioxide (bicarbonate)
COMP	cartilage-oligo matrix protein
CRO	Contract Research Organization, IQVIA (former Quintiles IMS)
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CTA	clinical trial application
CTX-II	C-terminal telopeptide of type II collagen
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EDTA	ethylenediaminetetraacetic acid
e.g.	for example
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

Abbreviation	Term
hCG	human chorionic gonadotropin
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HED	human equivalent dose
HIV	human immunodeficiency virus
hr	hour
IA	intra-articular
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
i.e.	that is
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IWR	interactive Web-based response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KOSS	Knee Osteoarthritis Scoring System
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LFT	liver function test
LSLV	last subject last visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
min	minute
mL	milliliter
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MSC	mesenchymal stem cell
N/A	not applicable
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NSAID	nonsteroidal anti-inflammatory drug
OA	osteoarthritis
PCD	primary completion date
PD	pharmacodynamic(s)
PGx	pharmacogenomic(s)
pH	potential of hydrogen
PI	Principal Investigator

Abbreviation	Term
PIB	powder in bottle
PIIANP	N-propeptide of type IIA collagen
PIINP	procollagen II N-terminal propeptide
PK	pharmacokinetic(s)
PR	pulse rate
PRG4	proteoglycan 4
PT	prothrombin time
QRS	QRS complex
QT	QT interval
QTc	corrected QT
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SOP	standard operating procedure
SOX9	sex-determining region Y-Box 9
Sponsor	California Institute for Biomedical Research (Calibr)
Sponsor's designated representative	CRO, i.e., IQVIA
SRSD	single reference safety document
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TBili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time to maximum observed plasma concentration
µg	microgram
ULN	upper limit of normal
US	United States
VAS	visual analog scale
vs	versus
WBC	white blood cell
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORMS	Whole-Organ Magnetic Resonance Imaging Score

Appendix 2. ACR Classification for OA of the Knee

Using history, physical examination, and radiographic findings:

Pain in the knee

And 1 of the following:

- Over 50 years of age
- Less than 30 minutes of morning stiffness
- Crepitus on active motion and osteophytes

(Altman, et al., 1986)

Appendix 3. Kellgren and Lawrence System for Classification of OA of the Knee

- Grade 0: No radiographic features of OA are present
- Grade 1: Doubtful joint space narrowing (JSN) and possible osteophytic lipping
- Grade 2: Definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
- Grade 3: Multiple osteophytes, definite JSN, sclerosis, possible bony deformity
- Grade 4: Large osteophytes, marked JSN, severe sclerosis and definite bony deformity

(Kellgren & Lawrence, 1957)