KOWA
RESEARCH INSTITUTE, INC.

A Phase II, Randomized, Double-blind, Active Comparator, Parallel Group Study to Evaluate the Efficacy and Safety of K-285 Compared with Menthol Gel for the Treatment of Delayed Onset Muscle Soreness (DOMS) in the Lower Extremity

Clinical Study Protocol

Drug Name:	K-285
Study Number:	K-285-201
U.S. IND Number:	IND135348
Protocol Original Version Date:	10 April 2020
Original Version #:	1.0
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Name of Sponsor:	**Kowa Research Institute, Inc.**
Address:	[redacted]
Managing Contract Research Organization (CRO):	[redacted]
Address:	[redacted]
Contact Numbers:	[redacted]
ClinicalTrials.gov	NCT04484428

INVESTIGATOR'S STATEMENT

I, the investigator, understand that all information concerning the product supplied to me by Kowa Research Institute, Inc. (KRI) and [redacted] in connection with this study and not previously published is confidential information. This information includes the Investigators' Brochure, protocol, case report forms, assay methods, technical methodology and basic scientific data.

I understand that any changes to the protocol must be approved in writing by KRI, [redacted] and the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before implementation, except where necessary to eliminate apparent immediate hazards to the subjects.

I confirm that I will report all adverse events (AEs) following the regulations indicated in the protocol.

I confirm that I will conduct this study in conformance with the principles of the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA), Good Clinical Practice (GCP), and the laws and regulations of the country where the study is to be conducted.

I confirm that I am informed of the need for record retention and that no data can be destroyed.

By my signature below, I hereby attest that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in this version of the protocol dated 10 April 2020.

Investigator's Signature: _____ Date: _____
mm/dd/yyyy

Printed Name: _____

SIGNATURE PAGE

[redacted]

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Date _____
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PROTOCOL SYNOPSIS

Name of Sponsor Company: Kowa Research Institute, Inc.	**Drug Under Study:** K-285	
Title of Protocol: A Phase II, Randomized, Double-blind, Active Comparator, Parallel Group Study to Evaluate the Efficacy and Safety of K-285 Compared with Menthol Gel for the Treatment of Delayed Onset Muscle Soreness (DOMS) in the Lower Extremity		
Protocol Number: K-285-201	**Phase:** II	**Indication:** Acute pain relief

Study Design:

This is a phase II, randomized, double-blind, active comparator, parallel group study to evaluate the efficacy and safety of K-285 compared with menthol gel for the treatment of delayed onset muscle soreness (DOMS) in the lower extremity. The study will consist of screening, an exercise visit (DOMS induction), in-patient and out-patient periods up to 3 weeks, and a follow-up telephone call.

During the Screening Visit, subjects will provide informed consent and complete screening assessments including medical history, identification of the dominant leg, physical and skin examinations, blood and urine tests, vital signs measurements, electrocardiogram (ECG), and other screening procedures. Subjects who are able to participate in the study (Period 1 and 2) and who meet the pre-exercise inclusion and exclusion criteria will be enrolled into the study and return to the clinic on Day -1.

Eligibility will be confirmed and enrolled subjects will perform a standardized repetitive quadriceps muscle exercise to create DOMS to both legs (Day -1). The exercise regimen will consist of a warm-up, determination of maximum tolerated weight, and timed and un-timed workout phases. Within 24 to 30 hours after the exercise session (Day 1), subjects will rate the pain of both legs using a categorical pain scale and record pain intensity of both legs at rest and while standing using a 0-100 point electronic visual analog scale (eVAS) (a capture program will linearly convert the pixel touched to an integer between 0 and 100) to determine eligibility for randomization. The specific post-exercise [redacted] inclusion criterion will be masked to subjects. [redacted]. If both legs meet post-exercise inclusion criteria, the study leg will be the dominant leg, based on hand dominance. Subjects not qualifying for randomization will be given appropriate standard of care.

A total of 240 subjects who meet post-exercise inclusion criteria will be randomly assigned in a 1:1 ratio to Treatment Arm A (K-285 gel) or Treatment Arm B (Menthol gel). [redacted]

[redacted]

In Period 1 [redacted] study gels will be applied to randomized subjects on a [redacted] on the study leg as follows:

- Treatment Arm A: Each subject will apply K-285 to the study leg.
- Treatment Arm B: Each subject will apply menthol gel to the study leg.

The first study gel application to the study leg will be applied by the subject with investigator (or designee) oversight to ensure proper application at the clinic on Day 1 within 24 to 30 hours after DOMS induction. Subsequent study gel applications at the clinic will be applied to the study leg by the subject with investigator (or designee) oversight to ensure proper application. On Day 2, photographic and residue evaluation of the application site will be performed prior to the [redacted] study gel application. Subjects will remain in the clinic until they are discharged following completion of study assessments on Day 2.

Pain intensity assessments will be performed for the study leg and non-study leg at rest and while standing using a 0-100 point eVAS on Day 1 at Baseline (0 hours) and at [redacted] after the first study gel application. Pain assessments scheduled between midnight and 6 am may be skipped if subjects are asleep but subjects may not skip more than two sequential assessments. A time window of +30 minutes will be allowed between qualification (baseline assessment) and first gel application (0 hour). The following time windows will be allowed for each pain assessment (eVAS, Perceptible Pain Relief, and Meaningful Pain Relief) time point: [redacted]

Following discharge from the clinic on Day 2, subsequent study gel applications and pain intensity assessments will be performed by the subject on an out-patient basis (Day 2 through Day 8). Subjects will be instructed not to shower or bathe for at least 30 minutes before and at least 1 hour after gel application. All pain intensity assessments including eVAS, Perceptible Pain Relief, and Meaningful Pain Relief will be recorded in e-diaries through Day 8 (Period 1), and all study gel applications and rescue medications will be recorded in the e-diary by the subject through Day 22 (Period 1 and 2). Perceptible Pain Relief and Meaningful Pain Relief will be recorded in the e-diary until achieved in Period 1. A telephone call will be conducted by study staff on Day 5 (±1 day) to assess safety. Subjects will return to the clinic for assessments on Day 8 (±1 day). For subjects who are assigned to receive study gel for 1 week, Day 8 end of

study (EOS) (+1 day) will be a clinic visit and a follow-up telephone call to assess safety will be conducted by study staff on Day 15 (±1 day). Subjects who are assigned to receive study gel for 3 weeks will continue to apply study gel on an out-patient basis from Day 8 to Day 22 (Period 2) according to their assigned dosing regimen ([redacted] (Table 1 above). For subjects who are dosing in Period 2, telephone calls to assess safety will be conducted by study staff on Day 11 (±1 day) and Day 18 (±1 day), study gel applications and use of any rescue medications will be recorded in e-diaries by the subjects through Day 22, and an end of study (EOS) clinic visit will occur on Day 22 (+1 day). A follow-up telephone call to assess safety will be conducted by study staff on Day 29 (±1 day).

Use of any rescue medication for DOMS is strongly discouraged until 168 hours (Day 8) after the first study gel application, at which time over-the-counter (OTC) acetaminophen (one 500 mg acetaminophen tablet twice daily, not more than every 6 hours) as rescue medication for DOMS is permitted if required. Subjects experiencing severe pain or inability to move or walk due to pain may be permitted to use rescue medication (one 500 mg OTC acetaminophen tablet twice daily, not more than every 6 hours) prior to 168 hours after the first study gel application. If subjects take rescue medication before the first 168 hours, it will be captured as a concomitant medication, and subjects will record their pain intensity in the e-diary before taking the rescue medication. The number of tablets taken and the date and time will be recorded in the e-diary.
When the [redacted]. The interim analysis will assess futility of the trial (conditional power <0.05). If futility is determined, the study will be terminated. If continuation of the trial is determined, subject enrollment will be resumed.

Primary Objective:

- To evaluate the efficacy of K-285 compared with menthol gel between 0 to 24 hours after the first gel application for the treatment of DOMS

Secondary Objectives:

- To evaluate the efficacy of K-285 compared with menthol gel after the first gel application for the treatment of DOMS
- To evaluate the safety and tolerability of K-285 compared with menthol gel after the first gel application for the treatment of DOMS

Subject Population:
The study population will be adult male and female subjects aged 18 to 35 years, inclusive, with a body mass index (BMI) between 18 and 32 kg/m^2, inclusive.

Number of Subjects:	**Number of Centers:**
Total 240 subjects with 120 subjects in each of the 2 treatment arms (Table 1 above).	1 site in the United States
Dose Levels: K-285: [redacted] Menthol gel: [redacted]	**Route of Administration:** Topical gel

Duration of Treatment:
[redacted] (Period 1): Each subject will apply [redacted] of study gel [redacted] [redacted] (Period 1 and 2): Each subject will apply [redacted] of study gel [redacted] and then will apply study gel [redacted]

Criteria for Evaluation:
Efficacy:

Primary Endpoint:

- The sum of pain intensity difference (SPID) between [redacted] for the study leg after the first study gel application while standing using a 0-100 point eVAS

Secondary Endpoints:

For both the study leg and the non-study leg

- SPID0-24 hours after the first study gel application at rest using a 0-100 point eVAS
- SPID between 0 (Baseline) to 12 hours (SPID0-12) after the first study gel application while standing using a 0-100 point eVAS
- SPID0-12 hours after the first study gel application at rest using a 0-100 point eVAS
- SPID between 0 (Baseline) to 48 hours (SPID0-48) after the first study gel application while standing using a 0-100 point eVAS
- SPID0-48 hours after the first study gel application at rest using a 0-100 point eVAS
- SPID between 0 (Baseline) to 72 hours (SPID0-72) after the first study gel application while standing using a 0-100 point eVAS
- SPID0-72 hours after the first study gel application at rest using a 0-100 point eVAS
- [redacted]

Safety:

Safety assessments will include adverse events (AEs), vital sign measurements (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature), ECG, physical examination findings including weight, study gel application site reactions, clinical laboratory test results, study gel use, and concomitant medication use.

Criteria for Inclusion:
Pre-exercise Criteria for Inclusion:

1. Subject must provide informed consent before any study-specific evaluation is performed.
2. Subject is male and female aged 18 to 35 years, inclusive.
3. Subject has a body mass index of 18 to 32 kg/m^2, inclusive

[redacted]

[redacted]

6. Subject hematology, serum chemistry, urinalysis, vital sign measurements (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature) and 12-lead ECG results show no clinically relevant abnormalities, as judged by the investigator at the Screening Visit.
7. All female subjects must have a negative serum pregnancy test result at screening and negative urine pregnancy test on Day -1 prior to admission to the clinic. Female subjects of childbearing potential must use one of the following acceptable birth control methods as specified before enrollment and throughout the study:
    a. Surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months before the first dose of study gel;
    b. Intrauterine device in place for at least 3 months before the first dose of study gel and throughout the study;
    c. Barrier method (condom or diaphragm) with spermicide for at least 14 days before the first dose of study gel and throughout the study;
    d. Surgical sterilization of the male partner (vasectomy at least 6 months before the first dose of study gel);
    e. Hormonal contraceptives for at least 3 months with a barrier method 14 days before the first dose of study gel and throughout the study;
    f. Abstinence.
8. Subject is able and willing to comply with the protocol and study procedures.
9. Subject has negative test results for drugs and alcohol at screening and is able and willing to abstain from marijuana and alcohol use for 4 days before Day 1 and throughout the study. Note that a positive screening result for marijuana is acceptable provided the subject will abstain for the study as described above.
10. Subject does not use nicotine or has quit using nicotine for at least 6 months before the first dose of study gel and will not use nicotine throughout the study.

[redacted]

[redacted]

Criteria for Exclusion:
Pre-exercise Criteria for Exclusion:

- [redacted]
- [redacted]

3. Subject has received oral or topical analgesic medications within 14 days before the Screening Visit.
4. Subject has used a systemic corticosteroid within 30 days before the Screening Visit.
5. Subject has a medical history that includes a contraindication for the use of menthol or nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., gastrointestinal ulcer, gastrointestinal bleeding).
6. Subject is taking medications or other substances contraindicated because of the nature of the study gel or the potential for drug interactions. This includes subjects with allergies to prescription or OTC products containing menthol or NSAIDs.

- [redacted]
- [redacted]
- [redacted]

14. Subject is pregnant or nursing.

15. Subject has participated in an investigational drug study within 30 days before Screening.
16. Subject is a member or a family member of the professional or ancillary personnel involved in the study.
17. Subject has participated in other clinical trials for K-285.
18. Subject has abnormal findings or assessments that are clinically noteworthy.
19. Subject who, in the opinion of the investigator, should not participate in the study.

Statistical Analysis:

In general, assessments with continuous outcomes will be summarized using the descriptive statistics n, mean, standard deviation (SD), median, minimum and maximum. For assessments with categorical outcomes, frequency counts and percentage will be calculated. Detailed statistical methodology will be presented in a separate statistical analysis plan.

Study Populations:

Three analysis populations will be evaluated:

- The full analysis set (FAS) will include all randomized subjects who have a baseline pain score, and at least 1 study gel applied
- The per-protocol set (PPS) will include all randomized subjects who have a baseline pain score, at least 1 study gel applied, and no major protocol violations.
- The safety set will include all subjects who have at least 1 study gel applied.

Primary Efficacy Analysis:

The primary analysis population is the FAS. The primary analysis will be repeated using the PPS. [redacted]. If there exist missing VAS values to be imputed, any such values will be imputed before calculating the SPID. After calculating the SPID, an analysis of covariance (ANCOVA) model will be applied for the primary endpoint with gender and treatment as main effects and baseline pain as a covariate.

Secondary Efficacy Analyses:

A mixed effect model repeated-measures (MMRM) with the same main effects and covariate will be applied to the PID while standing and PID at rest to investigate treatment differences. [redacted] The time to first dose of rescue medication, will be analyzed using the Kaplan-Meier method to estimate the survival distribution function.

Safety:

The safety endpoint data will be summarized for the safety set. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and serious AEs (SAEs) will be summarized by treatment group for overall number of AEs, severity, and relationship to study gel. The incidence of AEs will be summarized by body system and treatment group. The incidence of treatment-emergent AEs (TEAEs) will also be summarized by system organ class and preferred term. Clinical laboratory results will be summarized by treatment group along with change from Baseline. Vital sign measurements will be summarized by group and time point along with change from Baseline. All AE, clinical laboratory, vital sign, physical examination, study gel application site reaction, study gel use and concomitant medication use will be presented in data listings.

[redacted]

Sample Size Calculation:
The parameters are conservatively estimated based on the DOMS study with [redacted] gel. The between-group difference in the mean [redacted] is 11.07 with a SD of 25.62. To have statistical power of 90%, 113 subjects per group are required. Taking into account information loss caused by missing data, it is estimated that 120 subjects need to be treated with each study gel.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

API	active pharmaceutical ingredients
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
[redacted]	[redacted]
BMI	body mass index
CFR	Code of Federal Regulations
CK	creatine kinase
CK-MB	creatine kinase-myocardial band
CK-MM	creatine kinase in skeletal muscle
C_{max}	maximum concentration
COX(-2)	cyclooxygenase inhibitors
CRF	case report/record form
CRO	Contract Research Organization
DOMS	delayed onset muscle soreness
ECG	electrocardiogram
eCRF	electronic Case Report/Record Form
e-diary	electronic diary device
eVAS	electronic visual analog scale
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board

KRI	Kowa Research Institute, Inc.
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MAR	missing at random
MDMA	3,4-methylenedioxy-methamphetamine (Ecstasy)
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTW	Maximum tolerated weight
NSAID	non-steroidal anti-inflammatory drug
OTC	over-the-counter
PCP	phencyclidine
PID	pain intensity difference
PK	pharmacokinetics
PPS	per-protocol set
[redacted]	[redacted]
SAE	Serious Adverse Event
SD	standard deviation
SOP	Standard Operating Procedure/s
SPID	sum of pain intensity difference
SPID0-12	sum of pain intensity difference over 12 hours after the first gel application
SPID0-24	sum of pain intensity difference over 24 hours after the first gel application
SPID0-48	sum of pain intensity difference over 48 hours after first gel application
SPID0-72	sum of pain intensity difference over 72 hours after first gel application
[redacted]	[redacted]
STE	short time exposure
SUSAR	Serious Unexpected Suspected Adverse Reaction
TEAE	Treatment-emergent AE
TRP	transient receptor potential
VAS	Visual Analog Scale

1.0 INTRODUCTION AND RATIONALE FOR DOSE SELECTION

1.1 BACKGROUND INFORMATION

Non-steroidal anti-inflammatory drugs (NSAIDs), including non-selective NSAIDs and the more selective cyclooxygenase (COX-2) inhibitors, are extensively used in the United States and rest of world for the relief of pain and the reduction of inflammation. This class of medications is the most widely used when prescription and over-the-counter (OTC) products are considered. However, its oral use is not without risk, which most notably includes toxicity associated with gastrointestinal (GI) inflammation and bleeding.

Half of patients taking NSAIDs regularly have endoscopically confirmed gastric erosions, and 10%-30% have ulcers.[1] These risks are amplified in high risk groups, including the elderly, those with pre-existing gastropathy, chronic administration, concomitant corticosteroid use and Helicobacter pylori infection prior to NSAID therapy.[2] The use of selective COX-2 inhibitors, prudent use of proton pump inhibitors, and alternative medications have improved the incidence of gastropathy, but have not eliminated it. COX-2 inhibitors still demonstrate a significant risk of GI complications.[3]

The widespread use of OTC NSAIDs, which includes all non-selective COX inhibitors, poses a great risk of GI complications. Recent activity has also shown the potential for cardiovascular risk from the systemic use of COX-2 inhibitors, which was highlighted by the 2004 withdrawal of rofecoxib (Vioxx®). With this background, there is a need for safer alternatives to orally administered NSAIDs, especially for those in higher risk groups, or those intolerant of orally administered NSAIDs.

Topical analgesics offer an alternative to the use of systemic NSAIDs for relief of focal pain and inflammation. These fall into several categories, including anesthetics, counterirritants and analgesics. The first two categories are illustrated by the approved lidocaine 5% patch (Lidoderm®), and capsaicin, respectively. Flector® (diclofenac epolamine topical patch 1.3%) is an example of a prescription NSAID analgesic patch. A meta-analysis of 26 double-blind placebo-controlled NSAIDs trials that enrolled 2,853 patients demonstrated that in 19/26 trials the NSAID was superior to placebo and was shown to be safe.[4]

l-Menthol is a naturally occurring cyclic monoterpene alcohol of plant origin. Its use extends from culinary items to cosmetic products to pharmaceutical ingredients. With regards to its medicinal purposes, both prescribed and OTC menthol containing medications are currently available throughout the world for a host of conditions, including respiratory diseases, GI disorders, common cold, and musculoskeletal pain. It is also commonly used as part of analgesic, antiseptic, topical antipruritic, and counterirritant products. Its ability to modulate Transient Receptor Potential (TRP) cation channels and numerous other ion channels may underlie its reputed analgesic effects.[5] Menthol-containing OTC medications are currently marketed in the US as topical analgesics at concentrations up to 16% l-menthol in the US.

1.2 RATIONALE FOR STUDY AND DOSE SELECTION

Kowa Company Ltd. has developed K-285, a product containing [redacted] for relief of pain due to muscle soreness, sprains and strains.

The active pharmaceutical ingredients (API) in K-285 topical gel are [redacted] The menthol gel contains [redacted].

[redacted]

The most commonly reported treatment-related, treatment-emergent adverse events (TEAEs) (i.e., those reported by more than 2 subjects overall) were application site pain, application site erythema, application site discoloration, application site exfoliation, application site pruritus, and application site dryness. All TEAEs reported were mild in severity. There were no moderate or severe TEAEs, serious adverse events (SAEs), or deaths reported during the study. One subject (6.7%) discontinued from the study due to a treatment-related TEAE of application site discharge. All TEAEs were resolved by the end of the study. Dermatological findings related to the application site were reported as TEAEs, but these events and clinical laboratory assessments, vital sign measurements, electrocardiogram (ECG) assessments, and physical examinations were not considered clinically significant. Multiple applications of K-285 were safe and generally well tolerated by healthy subjects in this study.

Based on the Phase 1 study results, the dosage of K-285, [redacted]), showed higher [redacted], and thus was selected to evaluate efficacy and safety at 1 week (Period 1). For Period 2, both the [redacted] dosing regimens were selected to evaluate the additional safety profile at 2 weeks.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of K-285 compared with menthol gel between 0 to 24 hours after the first gel application for the treatment of delayed onset muscle soreness (DOMS).

2.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the efficacy of K-285 compared with menthol gel after the first gel application for the treatment of DOMS
- To evaluate the safety and tolerability of K-285 compared with menthol gel after first gel application for the treatment of DOMS

2.3 PRIMARY EFFICACY ENDPOINT

Primary Endpoint:

- The sum of pain intensity difference ([redacted] for the study leg after the first study gel application while standing using a 0-100 point electronic visual analog scale (eVAS)

2.4 SECONDARY EFFICACY ENDPOINTS

Secondary Endpoints:

<u>For both the study leg and the non-study leg</u>

- SPID0-24 hours after the first study gel application at rest using a 0-100 point eVAS
- SPID between 0 (Baseline) to 12 hours (SPID0-12) after the first study gel application while standing using a 0-100 point eVAS
- SPID0-12 hours after the first study gel application at rest using a 0-100 point eVAS
- SPID between 0 (Baseline) to 48 hours (SPID0-48) after the first study gel application while standing using a 0-100 point eVAS
- SPID0-48 hours after the first study gel application at rest using a 0-100 point eVAS
- SPID between 0 (Baseline) to 72 hours (SPID0-72) after the first study gel application while standing using a 0-100 point eVAS
- SPID0-72 after the first study gel application at rest using a 0-100 point eVAS

[redacted]

[redacted]

2.5 SAFETY ENDPOINTS

Safety assessments will include adverse events (AEs), vital sign measurements (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature), ECG, physical examination findings including weight, study gel application site reactions (including via an irritation rating scale), clinical laboratory test results, study gel use, and concomitant medication use.

3.0 STUDY DESCRIPTION

3.1 STUDY DESIGN

This is a phase II, randomized, double-blind, active comparator, parallel group study to evaluate the efficacy and safety of K-285 compared with menthol gel for the treatment of DOMS in the lower extremity.

The study will consist of screening, an exercise visit (DOMS induction), in-patient and out-patient periods up to 3 weeks, and a follow-up telephone call. During the Screening Visit, subjects will provide informed consent and complete screening assessments including medical history, identification of the dominant leg as determined by hand dominance, physical and skin examinations, blood and urine tests, vital signs measurements, ECG, and other screening procedures. Subjects who are able to participate in the study (Period 1 and 2) and who meet the pre-exercise inclusion and exclusion criteria will be enrolled into the study and return to the clinic on Day -1. Eligibility will be confirmed and enrolled subjects will perform a standardized repetitive quadriceps muscle exercise to create DOMS to both legs (Day -1). The exercise regimen will consist of a warm-up, determination of maximum tolerated weight, and timed and un-timed workout phases.

Within 24 to 30 hours after the exercise session (Day 1), subjects will rate the pain of both legs using a categorical pain scale and record pain intensity of both legs at rest and while standing using a 0-100 point eVAS (a capture program will linearly convert the pixel touched to an integer between 0 and 100) to determine eligibility for randomization. The specific post-exercise [redacted] inclusion criterion will be masked to subjects. [redacted] If both legs meet post-exercise inclusion criteria, the study leg will be the dominant leg, based on hand dominance. Subjects not qualifying for randomization will be given appropriate standard of care. A total of 240 subjects who meet post-exercise inclusion criteria will be randomly assigned in a 1:1 ratio to Treatment Arm A (K-285 gel) or Treatment Arm B (Menthol gel). [redacted]

[redacted]

In Period 1 ([redacted] on the study leg as follows:

- Treatment Arm A: Each subject will apply K-285 to the study leg.
- Treatment Arm B: Each subject will apply menthol gel to the study leg.

The first study gel application to the study leg will be applied by the subject with investigator (or designee) oversight to ensure proper application at the clinic on Day 1 within 24 to 30 hours after DOMS induction. Subsequent study gel applications at the clinic will be applied to the study leg by the subject with investigator (or designee) oversight to ensure proper application. On Day 2, photographic and residue evaluation of the application site will be performed prior to the [redacted] study gel application. Subjects will remain in the clinic until they are discharged following completion of study assessments on Day 2. Pain intensity assessments will be performed for the study leg and non-study leg at rest and while standing using a 0-100 point eVAS on Day 1 at Baseline (0 hours) and at [redacted] after the first study gel application. Pain assessments scheduled between midnight and 6 am may be skipped if subjects are asleep but subjects may not skip more than two sequential assessments. A time window of +30 minutes will be allowed between qualifying pain assessments and first study gel application (0 hours).

The following time windows will be allowed for each pain assessment (eVAS, Perceptible Pain Relief, and Meaningful Pain Relief) time point: ±15 minutes for assessments from 1 to 12 hours (Day 1), -20 minutes to +30 minutes for assessments at 18 through 24 hours (Day 2), and -20 minutes to +1 hour for assessments at 36 to [redacted] ([redacted] Following discharge from the clinic on Day 2, subsequent study gel applications and pain intensity assessments will be performed by the subject on an out-patient basis (Day 2 through Day 8). Subjects will be instructed not to shower or bathe for at least 30 minutes before and at least 1 hour after gel application.

All pain intensity assessments including eVAS, Perceptible Pain Relief, and Meaningful pain relief will be recorded in e-diaries through Day 8 (Period 1), and all study gel applications and rescue medications will be recorded in the e-diary by the subject through

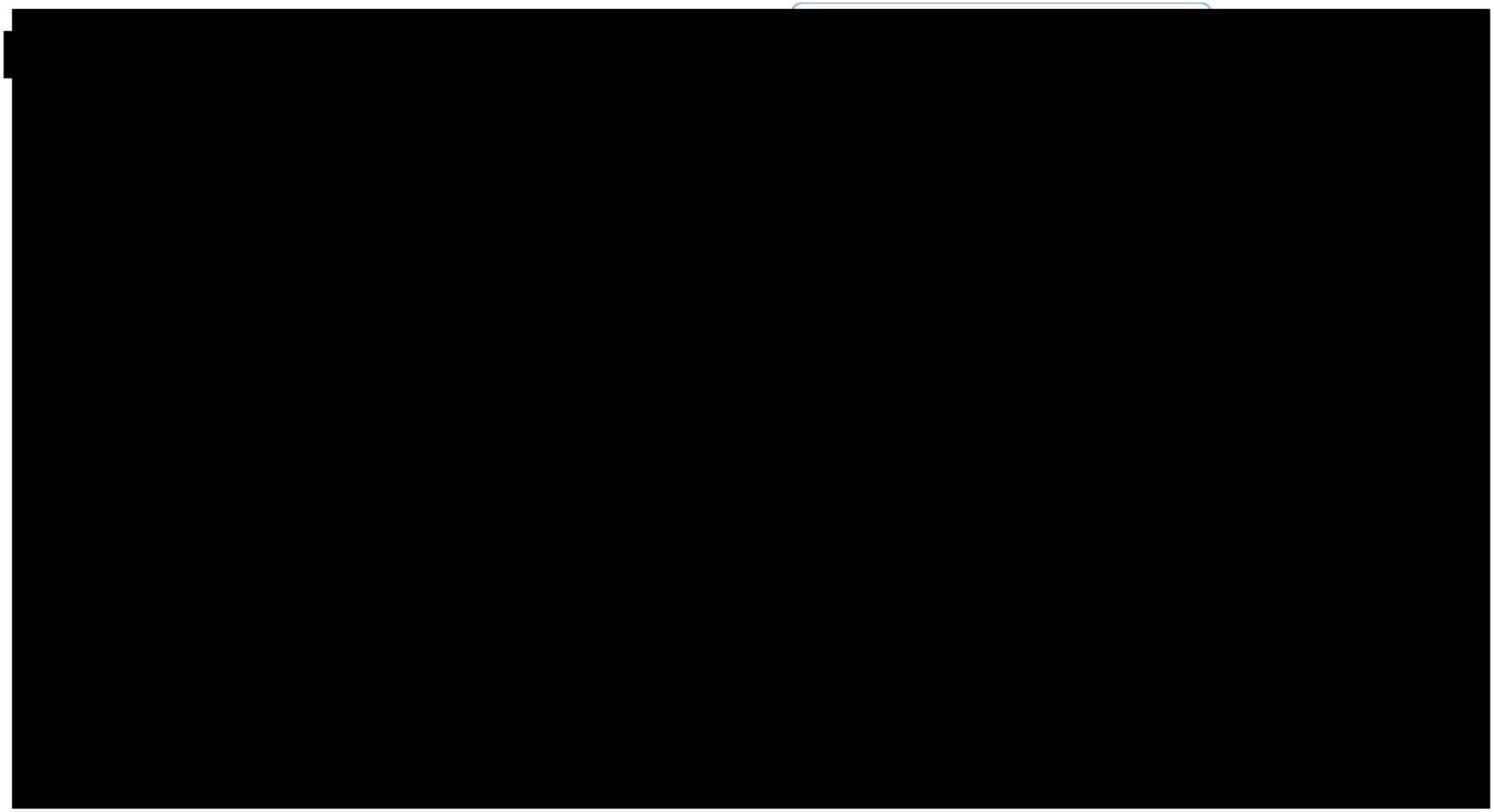
Day 22 (Period 1 and 2). Perceptible Pain Relief and Meaningful Pain Relief will be recorded in the e-diary until achieved in Period 1. A telephone call will be conducted by study staff on Day 5 (±1 day) to assess safety. Subjects will return to the clinic for assessments on Day 8 (±1 day). For subjects who are assigned to receive study gel for 1 week, Day 8 (+1 day) will be an end of study (EOS) clinic visit and a follow-up telephone call to assess safety will be conducted by study staff on Day 15 (±1 day). Subjects who are assigned to receive study gel for 3 weeks will continue to apply study gel on an out-patient basis from Day 8 to Day 22 (Period 2) according to their assigned dosing regimen ([redacted]) (Table 1: Treatment Assignment). For subjects who are dosing in Period 2, telephone calls to assess safety will be conducted by study staff on Day 11 (±1 day) and Day 18 (±1 day), study gel applications and use of any rescue medications will be recorded in e-diaries by the subjects through Day 22, and an end of study (EOS) clinic visit will occur on Day 22 (+1 day). A follow-up telephone call to assess safety will be conducted by study staff on Day 29 (±1 day).

Use of any rescue medication for DOMS is strongly discouraged until [redacted] after the first study gel application, at which time over-the-counter (OTC) acetaminophen (one 500 mg acetaminophen tablet twice daily, not more than every 6 hours) as rescue medication for DOMS is permitted if required. Subjects experiencing severe pain or inability to move or walk due to pain may be permitted to use rescue medication (one 500 mg OTC acetaminophen tablet twice daily, not more than every 6 hours) prior to 168 hours after the first study gel application. If subjects take rescue medication before the first 168 hours, it will be captured as a concomitant medication, and subjects will record their pain intensity in the e-diary before taking the rescue medication. The number of tablets taken and the date and time will be recorded in the e-diary.

[redacted] The interim analysis will assess futility of the trial (conditional power <0.05). If futility is determined, the study will be terminated. If continuation of the trial is determined, subject enrollment will be resumed.

A study schematic is shown in Figure 1. The schedule of assessments is shown in Table 2.

[redacted]



[redacted]

Table 2: Clinical Evaluation Schedule

ASSESSMENTS PERFORMED	Screening Visit	Exercise Visit	Period 1			Period 2				EOS Visit/ET[k]	Follow-up call
			In patient		Out patient	Safety Visit	Out patient	Safety Visit	Out patient		
Day	-30 to -2	-1	1	2	3-8	8 (±1 day)	9-14	15 (±1 day)	16-22	8 or 22 (+1 day)	15 or 29 (±1 day)
Informed consent	X										
Demography	X										
Medical/medication history	X	X									
Pre-exercise inclusion criteria, exclusion criteria	X	X									
Admission to clinic[a]			X								
Discharge from clinic[a]				X							
Visit to clinic (one day)	X	X				X		X		X	
Telephone Call (Days 5, 11, 18, and Day 15 or 29)[b]					X		X		X		X
Pre-exercise pain assessment (paper VAS)		X									
DOMS induction exercise		X									
e-diary, study training		X									
Issue e-diary			X								
eVAS qualifying pain assessments[c] (e-diary)			X								

ASSESSMENTS PERFORMED	Screening Visit	Exercise Visit	Period 1			Period 2				EOS Visit/ET[k]	Follow-up call
			In patient		Out patient	Safety Visit	Out patient	Safety Visit	Out patient		
Day	-30 to -2	-1	1	2	3-8	8 (±1 day)	9-14	15 (±1 day)	16-22	8 or 22 (+1 day)	15 or 29 (±1 day)
Categorical qualifying pain assessments[c] (e-diary)			X								
Post-exercise inclusion criteria			X								
Randomization			X								
Height and weight	X										
Vital signs[d]	X	X	X	X		X		X		X	
Electrocardiogram	X	X								X	
Physical examination	X	X				X		X		X	
Skin examination / assessment at study gel site	X	X	X	X		X		X		X	
Pregnancy test[e]	X	X								X	
Urine drug screen and alcohol test	X	X									
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X									X	
eVAS pain intensity assessments[c] (e-diary)			X	X	X	X				(X)[1]	
Perceptible and Meaningful pain relief assessments[c] (e-diary)			X							(X)[1]	
Photographic and residue evaluation[f]				X							

ASSESSMENTS PERFORMED	Screening Visit	Exercise Visit	Period 1			Period 2				EOS Visit/ET[k]	Follow-up call
			In patient		Out patient	Safety Visit	Out patient	Safety Visit	Out patient		
Day	-30 to -2	-1	1	2	3-8	8 (±1 day)	9-14	15 (±1 day)	16-22	8 or 22 (+1 day)	15 or 29 (±1 day)
Photographic evaluation of application site reactions[g]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Dispense study gel				X		X		X			
Apply study gel[h]			X	X	X	X	X	X	X	(X)	
Record adverse events	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications[i]	X	X	X	X	X	X	X	X	X	X	X
Record rescue medication use[j] (e-diary)			X	X	X	X	X	X	X	X	
Collect study gel										X	
Collect subject e-diary										X	

[redacted]; DOMS, delayed onset muscle soreness; e-diary, electronic diary device; EOS, end of study; ET, early termination; [redacted] a[redacted]; VAS, visual analog scale; (X), performed as indicated in the footnote.

a Subjects will enter the clinic on Day 1 and will be discharged on Day 2 after study assessments at [redacted] study gel application are completed.

b Study staff will contact subjects by telephone for assessment of AEs, skin condition and concomitant medications, and use of rescue medication. All subjects will be contacted on Day 5 (±1 day). Subjects participating in Period 1 will be contacted on Day 15 (±1 day). Subjects participating in Period 2 will be contacted on Day 11 (±1 day), Day 18 (±1 day), and Day 29 (±1 day).

c VAS and categorical qualifying pain assessments will be performed on both legs within 24-30 hours of exercise to induce DOMS. Pain intensity assessments (eVAS, Perceptible Pain Relief, and Meaningful Pain Relief) will be performed for the study leg and non-study leg at rest and while standing using a 0-100 point eVAS on Day 1 at Baseline (0 hours) and at [redacted] after the first study gel application. Baseline (0 hours) is the time point for the first study gel application; a time window of +30 minutes will be allowed between qualifying pain assessments (qualifying post-exercise inclusion criteria) and first study gel application (0 hour). The following time windows will be allowed for each pain assessment (eVAS, Perceptible Pain Relief, and Meaningful Pain Relief) time point: ±15 minutes for assessments from 1 to 12 hours (Day 1), -20 minutes to +30 minutes for assessments at 18 through 24 hours (Day 2), and -20 minutes to +1 hour for assessments at 36 to 168 hours (Day 2 to 8). Time to perceptible and meaningful pain relief will be recorded by subjects in their e-diary until achieved in Period 1. When study gel application and pain assessment occur at the same time point, pain assessments will be performed before study gel application.

d Vital sign measurements will include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature. Blood pressure and pulse rate will be measured after the subject has been resting in the supine position for at least 5 minutes.

e Serum pregnancy test at Screening and urine pregnancy test at Exercise visit, EOS Visit (Day 8 or Day 22) (females only).

f Photographic and residue evaluations of the application site will be performed before the [redacted] study gel applications on Day 2.

g Beginning with the [redacted] when an application site reaction is observed at the clinical site, photographs of the application site will be taken by site staff to visually document the skin condition at the site of gel application. If needed, the photographs will be periodically taken to follow-up the application site reaction. If an application site reaction is observed at home, photographs of the application site will be taken by site staff when subject returns to the clinical site. All photographs should be taken prior to gel a[redacted]

h [redacted]

The following time windows will be allowed for each study gel application time point: +30 minutes for first study gel application (0 hour) after qualifying pain assessments, ±15 minutes for the [redacted] applications, -20 minutes to +30 minutes for the [redacted] applications, and -20 minutes to +1 hour for other application time points.

At the site, study gel is applied to the study leg by the subject with investigator (or designee) oversight to ensure proper application. Following discharge from the clinic on Day 2, subsequent study gel applications will be performed by the subject. For subjects participating only in Period 1, the last application of study gel is applied at 6 am on Day 8. For subjects participating in Period 2, the last application of study gel is applied at 6 am on Day 22.

i All medications and other treatments taken by subjects within 30 days before dosing and during the study will be recorded in the eCRF. Any changes in the concomitant medications after discharge from the clinic on Day 2, either prescribed or self-administered, will be documented and reviewed during telephone calls, Safety visits and at the EOS Visits.

j Subjects will record all rescue medication use in the e-diary and it will be entered into the eCRF as a concomitant medication.

k For subjects participating only in Period 1 EOS is on Day 8 (+1 day), for subjects participating in Period 2 EOS is on Day 22 (+1 day). Note that EOS visits have a window of +1 day whereas Safety visits have a window of ±1 day.

l For Day 8, Period 1.

4.0 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

Subjects who do not meet eligibility criteria will be classified as screen failures and the reason(s) will be recorded in the case report form (CRF)/electronic CRF (eCRF).

4.1 INCLUSION CRITERIA

4.1.1 Pre-exercise Inclusion Criteria

Subjects are eligible for the study if all of the following criteria are met:

1. Subject must provide informed consent before any study-specific evaluation is performed.
2. Subject is male and female aged 18 to 35 years, inclusive.
3. Subject has a body mass index (BMI) of 18 to 32 kg/m^2, inclusive

[redacted]

6. Subject hematology, serum chemistry, urinalysis, vital sign measurements (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature) and 12-lead ECG results show no clinically relevant abnormalities, as judged by the investigator at the Screening Visit.
7. All female subjects must have a negative serum pregnancy test result at Screening and negative urine pregnancy test on Day -1 prior to admission to the clinic. Female subjects of childbearing potential must use one of the following acceptable birth control methods as specified before enrollment and throughout the study:
   a. Surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months before the first dose of study gel;
   b. Intrauterine device in place for at least 3 months before the first dose of study gel and throughout the study;
   c. Barrier method (condom or diaphragm) with spermicide for at least 14 days before the first dose of study gel and throughout the study;
   d. Surgical sterilization of the male partner (vasectomy at least 6 months before the first dose of study gel);
   e. Hormonal contraceptives for at least 3 months with a barrier method 14 days before the first dose of study gel and throughout the study;
   f. Abstinence.
8. Subject is able and willing to comply with the protocol and study procedures.
9. Subject has negative test results for drugs and alcohol at screening and is able and willing to abstain from marijuana and alcohol use for 4 days before Day 1 and throughout the study. Note that a positive screening result for marijuana is acceptable provided the subject will abstain for the study as described above.

10. Subject does not use nicotine or has quit using nicotine for at least 6 months before the first dose of study gel and will not use nicotine throughout the study.

[redacted]

4.2 EXCLUSION CRITERIA

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

[redacted]

3. Subject has received oral or topical analgesic medications within 14 days before the Screening Visit.
4. Subject has used a systemic corticosteroid within 30 days before the Screening Visit.
5. Subject has a medical history that includes a contraindication to the use of menthol or NSAIDs (e.g., gastrointestinal ulcer, gastrointestinal bleeding).
6. Subject is taking medications or other substances contraindicated because of the nature of the study gel or the potential for drug interactions. This includes subjects with allergies to prescription or OTC products containing menthol or NSAIDs.

[redacted]

[redacted]

14. Subject is pregnant or nursing.
15. Subject has participated in an investigational drug study within 30 days before Screening.
16. Subject is a member or a family member of the professional or ancillary personnel involved in the study.
17. Subject has participated in other clinical trials for K-285.
18. Subject has abnormal findings or assessments that are clinically noteworthy.
19. Subject who, in the opinion of the investigator, should not participate in the study.

4.3 DISCONTINUATION AND WITHDRAWAL CRITERIA

Subjects may voluntarily withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. The investigator may discontinue treatment of a subject or withdraw a subject from the study under specific circumstances, described below. The primary reason(s) for discontinuation or withdrawal (by the subject or the investigator) will be documented and recorded in the case report form CRF/eCRF.

The subject will be discontinued from study gel if any of the following occur:

1. There is a deterioration in the subject's signs/symptoms and/or the subject develops a disease or condition that in the opinion of the investigator, would compromise the subject's safety by continuing in the study.
2. In the investigator's judgment, it is in the subject's best interests.
3. Violation of the protocol inclusion and exclusion criteria.
4. The subject begins to take any medication(s) that is excluded by the protocol.
5. It is determined that there is discoloration, exfoliation or erosion, edema, discharge, blistering, exudate, ≥2 point on dermal responses score (Section 5.2.6), and/or any other dermal change that in the opinion of the investigator, would compromise the subject's safety by continuing in the study at the application site. The process for discontinuation due to an application site reaction is described in Section 4.3.1 below.
6. Occurrence of serious adverse event(s).
7. Pregnancy.

The subject will be withdrawn from the study if any of the following occur:

1. The subject withdraws consent.

2. The subject is lost to follow-up.
3. Any of the conditions are met in Section 6.5, Termination of the Study.
4. The subject is unable or unwilling to cooperate with study staff.
5. Death.

Subjects who discontinue or withdraw from the trial due to the above criteria or any other reason, will be encouraged to complete the final evaluations as detailed in Table 2. If a subject declines to complete early termination procedures, this decision will be recorded in the case report form CRF/eCRF.

If a subject discontinues or withdraws from the study due to an AE, the subject will be asked to return to the clinic for, at a minimum, the evaluations scheduled for the EOS/ET Visit (Day 8/Day 22). If the AE has still not resolved, additional follow-up will be performed, as appropriate, and documented in the subject's medical records. As a minimum requirement, AEs must be followed for 30 days after the subject's last dose of study gel or until resolution or until unresolved AEs are judged by the investigator (or designee) to have stabilized.

If subjects are lost to follow-up, attempts to contact them must be made and documented in the medical records. Subjects who fail to return for a study visit will be contacted directly by the study staff. A minimum of 2 documented phone calls will be made. If the study staff receives no response, they will send a certified letter requesting that the subject contact the study site regarding his or her status in the study.

Discontinued or withdrawn subjects will not be replaced.

4.3.1 Discontinuation due to an Application Site Reaction

1. During a clinical site visit, the application site reaction will be assessed by study staff. If there are any significant findings, they will be noted in each subject's source documents.
   - If the application site reaction is judged to meet the discontinuation criteria (Section 4.3), the subject will be discontinued from the study.

2. During the out-patient period at home, application site reactions will be assessed by the subject. If any application site reaction is noticed, the subject will contact the site before dosing.
   - The subject will not apply study gel until receiving confirmation from the site to proceed.
   - If the subject contacts the site and then the application site reaction is judged to meet the discontinuation criteria (Section 4.3), the subject will be discontinued from the study. At that time, the subject will be asked to gather safety reference information as follows:
     - Record the score of dermal response (Section 5.2.6) in the e-diary. Reference images of application site reactions are shown in Appendix 15.4.

5.0 PROCEDURES FOR EFFICACY AND SAFETY EVALUATIONS

5.1 EFFICACY EVALUATIONS

5.1.1 Pain Intensity

Prior to exercise to induce DOMS, pain will be assessed for both legs at rest and while standing using a 0-100 point paper VAS to exclude subjects with other pain.

Following exercise to induce DOMS, pain at rest and while standing will be assessed for both legs using a 0-100 point eVAS and a categorical pain scale to determine qualification for randomization and to identify the study leg (baseline assessment). All pain assessments will be recorded in the e-diary.

After randomization, pain at rest and while standing will be assessed for the study leg and the non-study leg using a 0-100 point eVAS at all post-study gel application time points in Period 1 (Table 2). When study gel application and pain assessment occur at the same time point, pain assessments will be performed before study gel application.

The subject will rest quietly for at least 5 minutes before assessing pain at rest for the study leg and non-study leg (the study leg will be assessed first). The subject will sit for at least 5 minutes, then stand up and rate the worst pain caused by standing (the act of moving from a sitting to standing position) for the study leg and non-study leg (the study leg will be assessed first).

5.1.1.1 *Visual Analog Scale*

The pain VAS, a unidimensional measure of pain intensity, is a continuous scale from 0 to 100 comprised of a horizontal line anchored by 2 descriptors, one for each symptom extreme: "no pain" (score of 0) and "worst possible pain" (score of 100). A paper version of the pain VAS will be used for pre-exercise pain assessments (Appendix 1).

The pain eVAS is electronically displayed and is completed by the subject for baseline and each post-randomization pain intensity assessment by touching the point on the eVAS that represents their pain intensity. (A capture program will linearly convert the pixel touched to an integer between 0 and 100). The integers of the eVAS will be referred to as points. The assessment date and time for the study leg and for the non-study leg is recorded in the e-diary (Appendix 1).

5.1.1.2 *Categorical Pain Scale*

A 4-point categorical pain scale (none, mild, moderate, severe) at rest will be used to assess pain intensity following the exercise session. A categorical pain scale is provided in Appendix 2.

5.1.2 Use of Rescue Medication

Use of any rescue medication for DOMS is strongly discouraged until 168 hours after the first study gel application, at which time OTC acetaminophen (one 500 mg acetaminophen tablet twice daily, not more than every 6 hours) as rescue medication is permitted if required.

Subjects experiencing severe pain, or inability to move or walk due to pain, may be permitted to use rescue medication (one 500 mg OTC acetaminophen tablet twice daily, not more than every 6 hours) prior to 168 hours after the first study gel application. If subjects take rescue medication within the first 168 hours after the first study gel application, it will be recorded in the e-diary as rescue medication, and entered into the eCRF as a concomitant medication, and will be programmatically categorized as a concomitant medication. Subjects will record their pain intensity in the e-diary before taking the rescue medication. The number of tablets taken and the date and time will be recorded in the e-diary.

5.1.3 Time to Onset of First Perceptible and Meaningful Pain Relief

Pain assessments of time to first perceptible pain relief and time to meaningful pain relief for both legs at rest and while standing will be recorded by subjects using their e-diary until achieved in Period 1. At the time of first perceptible pain relief and at the time of meaningful pain relief, subjects will use their e-diary to record the time the events are experienced. Since these assessments will be captured in the e-diary, the electronic database will be the direct point of data capture and will serve as source for this variable.

5.1.3.1 *Onset of Perceptible Pain Relief*

Onset of perceptible pain relief will be assessed for the study leg and non-study leg at rest and while standing by responding "*no*" or "*yes*" to a question such as the following example:

Please confirm that you would like to report that you have experienced perceptible pain relief at **REST**/while **STANDING** in your **STUDY/NON-STUDY** leg. Please note that "perceptible pain relief" means any pain relief at all. If you feel the pain is getting even a little bit better, then please answer "YES."

5.1.3.2 *Onset of Meaningful Pain Relief*

Onset of meaningful pain relief is assessed for the study leg and non-study leg at rest and while standing only after onset of perceptible pain relief has been achieved. The subject responds "*no*" or "*yes*" to a question such as the following example:

Please confirm that you would like to report that you have experienced meaningful pain relief at **REST/while STANDING** in your **STUDY/NON-STUDY leg.** Please note that "meaningful pain relief" is "When the relief from pain is meaningful or significant to you." This does not necessarily mean that you feel completely better, although you might. Remember to tell the Diary when you first experience meaningful pain relief.

5.2 SAFETY EVALUATIONS

5.2.1 Adverse Events

Adverse events will be recorded according to the schedule in Table 2. All AEs, whether ascribed to study procedures or not, will be documented on the eCRF and will include the date and time of onset, a description of the AE, severity, duration, actions taken, outcome, and the relationship between the study gel and the event. Any subject who discontinues/withdraws from the study due to an AE will be followed up until the outcome is determined and written reports are provided by the investigator. Adverse event

definitions, and reporting and follow-up requirements are described in Section 9.1, 9.2, and 9.3, respectively.

5.2.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed by a central laboratory. Blood samples will be collected according to the schedule in Table 2 and processed as detailed in the Laboratory Manual.

Urinalysis will be performed by a central laboratory according to the schedule in Table 2. Urine samples will be collected and processed as detailed in the Laboratory Manual. If microscopy is required, a urine sample will be sent to the local laboratory.

The parameters being measured are shown in Table 3.

Table 3. Clinical Laboratory Test Parameters

Hematology	Clinical Chemistry	Urinalysis
Basophils	Alanine aminotransferase	Bilirubin
Eosinophils	Albumin	Blood
Hematocrit (Packed cell volume)	Alkaline phosphatase	Glucose
	Aspartate aminotransferase	Ketones
	Bicarbonate	Leukocytes
Hemoglobin	Bilirubin (total)	Nitrites
Lymphocytes	Bilirubin (direct; only if total is elevated)	pH
Mean cell hemoglobin	Calcium	Protein
	Chloride	Specific gravity
Mean cell hemoglobin concentration	Creatine kinase[1]	Urobilinogen
	Creatinine	
Mean cell volume	Follicle-stimulating hormone (post-menopausal female patients only)	**At the discretion of the investigator based on urinalysis results**
Monocytes	Gamma glutamyl transferase	
Neutrophils	Triglycerides	Microbiology
Platelet count	Glucose (fasting)	Urine Microscopy
Red blood cell count	Human chorionic gonadotropin (all female patients)	
	Lactate dehydrogenase	
White blood cell count	Magnesium	
	Potassium	
	Phosphate (inorganic)	
	Protein (total)	
	Sodium	
	Blood urea nitrogen (BUN)	
	Uric acid	

[1] Elevated levels of creatine kinase are expected as a result of the exercise performed on Day -1 and will be handled as described in Section 5.2.2.1.

5.2.2.1 *Elevated Levels of Serum Creatine Kinase*

Elevations of serum creatine kinase (CK) are expected to occur as a consequence of the exercise performed on Day -1 and will not be reported as AEs. Additional safety steps will be taken to monitor the subjects for signs of rhabdomyolysis. If a subject has a serum CK above 10,000 U/L (and associated elevations of lactate dehydrogenase [LDH], aspartate aminotransferase [AST], or alanine aminotransferase [ALT]), but no significant signs or symptoms of rhabdomyolysis other than muscle pain and swelling at the exercised muscles,

the following actions will be taken with the subject until the EOS Visit (Day 8 for subjects dosing during Period 1 and Day 22 for subjects dosing during Period 2):

- Subjects will be instructed to monitor the urine for changes in color carefully.
- Subjects will be instructed to report any urine discoloration, such as dark yellow, brown, cola or tea colored urine, to study personnel.
- Subjects will be instructed to maintain adequate hydration at home (approximately 15.5 cups [3.7 liters] of fluids for males and 11.5 cups [2.7 liters] of fluids a day for females)

In addition, the following actions may be taken with the subject at the discretion of the investigator:

- Subjects will be asked to stay overnight at the study site where vigorous hydration will be administered and monitoring for any clinical signs or symptoms of rhabdomyolysis will be undertaken. The subject will be released when, per the investigator's discretion, it is appropriate to do so. Prior to release, the sponsor's Medical Monitor will be notified.
- Subjects will have a serum CK clinical laboratory repeated as clinically indicated.
- Subjects will have a urinalysis repeated as clinically indicated.

If there is an elevation in CK and rhabdomyolysis is suspected, the work-up should also include evaluation of CK Panels (total CK, CK-myocardial band [CK-MB], CK in skeletal muscle [CK-MM] and CK in brain [CK-BB]), troponin, creatinine, myoglobin (serum and urine), transaminases, total bilirubin levels, and urinalysis including urine sediment. A physical examination should be performed to document findings such as muscle tenderness, weakness, or rash. An ECG should also be performed. Abnormalities should be followed until they have returned to baseline, or until the investigator considers them clinically stable.

5.2.3 Vital Signs

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature. Blood pressure and pulse rate will be measured after the subject has been resting in the supine position for at least 5 minutes. Measurements will be performed according to the schedule in Table 2.

5.2.4 Electrocardiogram

The ECGs will be performed according to the schedule in Table 2.

5.2.5 Physical Examination

General physical examinations will be performed according to the schedule in Table 2. The examination will include the following: general condition, dermatologic, eyes, ears, nose, throat, neck, thyroid, heart, respiratory system, abdomen, kidneys, skeletal system, extremities, lymphatic system, nervous system.

5.2.6 Skin Examination (Application Site Reaction)

Skin examination will be performed according to the schedule in Table 2. The investigator or designee will assess the target application site to ensure that the skin is not broken or irritated before each study gel application and document the skin condition in the eCRF using following rating scales.

Dermal Responses
0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond application site
Notes: Papules are defined as solid, circumscribed skin elevations up to the size of a split pea (5 mm). Vesicles are defined as small blisters.

Other Effects (With Corresponding Numeric Score)
None (0) = no change in appearance
A (0) = slightly glazed appearance
B (1) = marked glazed appearance
C (2) = glazing with peeling and cracking
F (3) = glazing with fissures
G (4) = film of dried serous exudates covering all or part of the application site
H (5) = small petechial erosions and/or scabs

Subjects will be instructed to notify study staff if they experience any dryness, itching, burning, pain, soreness, or other symptom at the application site even during the out-patient period. If there are unscheduled visits due to AEs, the investigator will assess the target application site and all application site reactions will be recorded in the eCRF.

These signs of skin irritation will be included in the AE section of the eCRFs. If a subject is discontinued from the study due to an application site reaction, the AE will be followed to resolution or up to 30 days after the last dose, whichever comes first.

Subjects who discontinued due to application site reaction may undergo a patch test, at the discretion of the investigator.

Subjects who choose to discontinue from participating in the study will rate their dermal response in the e-diary. Dermal Responses scored by subjects will not be recorded in the eCRF.

5.2.7 Concomitant Medications
Concomitant medications will be recorded according to the schedule in Table 2.

5.3 OTHER EVALUATIONS
5.3.1 Demographics, Medical History and Other Baseline Characteristics
Demographics and other baseline characteristics (age, sex, race, ethnicity, height, and weight) as well as medical history information including identification of dominant leg, skin condition (history of rash, allergy, eczema, etc.) and any allergy history (including fragrance, jewelry, dust, clothing, house dust, animal, metal, rubber, nylon, food, pollen allergy, etc.) will be collected on all subjects at the Screening Visit.

5.3.2 Drug and Alcohol Screening

A urine drug screen and alcohol breath test, or alcohol saliva test, will be conducted according to the schedule in Table 2. Urine drug screen will include urine screen for cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine (PCP), benzodiazepines, barbiturates, methadone, oxycodone, 3,4-methylenedioxy-methamphetamine (MDMA or ecstasy), buprenorphine (BUP9), morphine, propoxyphene, and tricyclic antidepressants.

5.3.3 Pregnancy

All female subjects will have a serum pregnancy test at the Screening Visit. Subjects with a positive pregnancy test result will not be randomized. A urine pregnancy test will be performed at the Exercise visit and at the EOS/ET Visits (Day 8 or Day 22).

5.3.4 Standardized Exercise Regimen

All enrolled subjects will perform a standardized repetitive quadriceps muscle exercise consisting of warm-up, determination of maximum tolerated weight (MTW), and timed and untimed work-out phases, described below. Subjects will be instructed to stay well hydrated by increasing their water intake, minimizing caffeinated beverages, and avoiding alcohol during the exercise regimen.

1. Warm-up and determination of MTW

Subjects will complete a warm-up of 4 sets of 10 regular body weight squat exercises from standing position (2 sets without weights and 2 sets with approximately 10-20 pounds of weight). The MTW on the leg curl machine is then determined for each leg by having the subject do a full extension and flexion with resistance starting with a low but reasonable weight selected by the study staff and increasing it with every repetition until subjects reach their MTW. The MTW is defined as the highest weight under which a subject could perform a full extension and flexion.

2. Workout: timed phase

Starting with the dominant leg, subjects will perform 6 sets of 10 leg extension and flexion exercises with each leg on the curl machine under 80% of the MTW for that leg. Each repetition is performed through the full pain-free range of motion in a slow, controlled manner. Subjects perform the concentric portion of the repetition for 2 seconds, pause at full contraction for 1 second, and then complete the eccentric portion over a 4 second period (for a total of 7 seconds per repetition). Subjects perform each set as tolerated and are given a 1-2 minute rest period in between sets. Repetitions are performed until subjects are unable to move the weight load through the full range of motion. If subjects are unable to complete the full 6 sets under 80% MTW, the weight is decreased in 5 pound increments until subjects can no longer complete 60% MTW, or 6 sets are completed.

3. Workout: untimed phase

Subjects complete untimed flexion-and-extension exercises (15-20 repetitions) beginning with the last weight used in the timed phase. The weights are gradually decreased in increments of 5 pounds until no weight is used.

The same protocol is performed on the subject's opposite leg.

5.3.5 Photograph and Residue Evaluation

5.3.5.1 *Photographic Analysis*

To visualize the skin condition at the site of study gel application, photographs of the application site will be taken before the [redacted] study gel applications on [redacted]

Also, when an application site reaction is observed at the clinical site, photographs of the application site will be taken by site staff to visually document the skin condition at the site of gel application. Photographs may be taken periodically as needed to follow-up on the condition of the application site reaction. If an application site reaction is observed at home, photographs of the application site will be taken by site staff when subject returns to the clinical site.

Photographs should be taken at an angle of less than 45 degrees relative to the skin plane with the area of gel application closest to the digital camera. Each photograph will include a paper label in the photograph identifying the subject number, date, assessment time point, and initials of the photographer. The label will be placed on the skin adjacent to the gel application.

5.3.5.2 *Residue Evaluation*

To evaluate the subject's impression of the dried white gel residue, the following rating scale will be assessed before the fifth and sixth study gel applications on Day 2 and will be recorded on the appropriate form. Subjects must not shower, bathe, or wash the treated area until after discharge on Day 2.

The following rating scale will be used:

0 = No dried white residue was observed
1 = Dried white residue was observed but no discomfort.
2 = Dried white residue was observed and slight discomfort (between 1 and 3)
3 = Dried white residue was observed and uncomfortable

5.4 TOTAL BLOOD VOLUME

The total blood volume planned for collection during the study will be described in the informed consent form (ICF).

6.0 CONDUCT OF STUDY

6.1 STUDY BLINDING AND RANDOMIZATION

The study will be double-blind. The investigator, subjects, and sponsor personnel involved in the monitoring or conduct of the study will be blinded to the identity of the treatment from the time of randomization until the time of unblinding. Unblinding will only occur in the case of subject emergencies (Section 7.8) and at the conclusion of the study. Study staff will instruct subjects not to talk about their study medication, their pain intensity, study design etc., among subjects.

[redacted] will prepare the randomization schedule before the study. Enrolled, eligible subjects will receive a kit containing study gels according to an allocation table that randomly assigns subjects by order of enrollment to receive study gel for [redacted] in 1 of 2 treatment arms (A or B)

(Section 7.2). Separate allocation tables will be prepared for 120 male and 120 female subjects. Male or female enrollment may exceed the target sample size (n=120 each gender) by ±10%. If the target sample size is exceeded in one gender, the next available kit number in the other gender will be assigned.

The identity of the study gels in the treatment arms will be masked by having identical appearance, packaging, labeling and schedule of administration. Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of unblinding.

6.2 SUBJECT INFORMED CONSENT

Written consent will be obtained from the subject prior to any study specific procedure or investigation.

Information about the study will be given to the subject both verbally and in writing. The written subject information will explain the objectives of the study, its potential risks and benefits. The subject must have adequate time to read the information and to ask the investigator any questions. The investigator must be satisfied that the subject has understood the information provided before written consent is obtained. If there is any doubt as to whether the subject has understood the written and verbal information, the subject should not enter the study.

Participating subjects will be asked to sign and date an ICF, the original copy of which will be kept by the investigator. A copy of the signed ICF will be given to the subject. A record will be made in the notes that the subject voluntarily agreed to participate in the study. The original signed ICF must be made available to the study monitor for inspection.

6.3 STUDY VISITS

Note: Timing of procedures and assessments are provided as examples. Actual timing may vary for each subject. Time points and time windows for study gel application and pain assessments are described in Table 2.

- Day -30 to Day -2:
  - Screening Visit: The Screening Visit at the clinic to determine subject eligibility can take place anytime within this time period. Assessments include the following:
    - Informed consent
    - Demographics
    - Medical/medication history
    - Pre-exercise inclusion criteria, exclusion criteria
    - Height and weight
    - Vital signs
    - ECG
    - Physical examination
    - Skin examination / assessment at study gel site of both legs
    - Pregnancy test (serum) (females only)
    - Urine drug screen and alcohol test
    - Clinical laboratory tests (hematology, serum chemistry, and urinalysis)
    - Record AEs
    - Record concomitant medications
- Day -1:
  - Exercise Visit: On Day -1 procedures and assessments are as follows:
    - Update Medical/medication history
    - Pre-exercise inclusion and exclusion criteria
    - Pain assessment (pre-exercise to exclude subjects with other pain using a paper VAS)
    - DOMS induction exercise
    - Vital signs
    - ECG
    - Physical examination
    - Skin examination / assessment at study gel site of both legs
    - e-diary, study training

- Urine drug screen and alcohol test
- Pregnancy test (urine) (females only)
- Record AEs
- Record concomitant medications
- Subjects return home after completing procedures and assessments

- Day 1 to Day 2
  - Admission Visit: On Day 1, subjects will be admitted to the clinic. Day 1 procedures and assessments are as follows:
    - Issue e-diary (subjects will record eVAS and Categorical Qualifying Pain Assessments in e-diary prior to randomization)
    - VAS Qualifying Pain assessment. Note: Time 0 hours is the baseline time point for the first study gel application and occurs within 30 minutes of qualifying pain assessments (post-exercise inclusion criteria).
    - Categorical Qualifying Pain assessment. Note: Time 0 hours is the baseline time point for the first study gel application and occurs within 30 minutes of qualifying pain assessments (post-exercise inclusion criteria).
    - Post-exercise inclusion criteria
    - Randomization (for subjects who meet post-exercise eligibility criteria)
    - Vital signs
    - Skin examination / assessment at study gel site
    - Apply study gel according to treatment schedule
    - VAS pain intensity assessment (before study gel application when study gel application and pain assessment occur at the same time point).
    - Perceptible and meaningful pain relief assessments (before study gel application when study gel application and pain assessment occur at the same time point). Pain assessments of time to first perceptible and meaningful pain relief for both legs at rest and while standing will be recorded by subjects until achieved in Period 1.
    - Photographic evaluation of application site reactions, as needed (before study gel application, beginning with the second study gel application)
    - Record AEs
    - Record concomitant medications
    - Record rescue medication

- Day 2 procedures and assessments are as follows:
  - Vital signs
  - Skin examination / assessment at study gel site
  - VAS pain intensity assessment (before study gel application when study gel application and pain assessment occur at the same time point)
  - Perceptible and meaningful pain relief assessments (before study gel application when study gel application and pain assessment occur at the same time point). Pain assessments of time to first perceptible and meaningful pain relief for both legs at rest and while standing will be recorded by subjects until achieved in Period 1.
  - Photographic and residue evaluation (before the fifth and sixth study gel applications)
  - Photographic evaluation of application site reactions, as needed (before study gel application)
  - Apply study gel according to treatment schedule
  - Record AEs
  - Record concomitant medications
  - Record rescue medication
  - Dispense study gel (for out-patient portion)
  - Discharge from the clinic (after study assessments at 24 hours and the sixth study gel application are completed)

- Day 3 to Day 8
  - Out-patient portion Period 1: Subjects apply study gel according to their assigned treatment and record assessments as follows:

- VAS pain intensity assessment (before study gel application when study gel application and pain assessment occur at the same time point)
- Perceptible and meaningful pain relief assessments (before study gel application when study gel application and pain assessment occur at the same time point). Pain assessments of time to first perceptible and meaningful pain relief for both legs at rest and while standing will be recorded by subjects until achieved in Period 1.
- Photographic evaluation of application site reactions, as needed (before study gel application)
- Apply study gel according to treatment schedule
- Record AEs
- Record concomitant medications
- Record rescue medication use

- Day 5 (±1 day):
  - Telephone Call Period 1 to assess safety and skin condition.
    - Record AEs
    - Record skin condition if applicable.
    - Record concomitant medications
    - Record rescue medication use
- Day 8:
  - EOS Visit Period 1 (+1 day). Procedures and assessments are as follows:

- Vital signs
- ECG
- Pregnancy test (urine) (females only)
- Clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Physical examination
- Skin examination / assessment at study gel site
- [redacted]
- [redacted]
- Apply study gel at 6 am on Day 8
- Photographic evaluation of application site reactions, as needed (before study gel application)
- Record AEs
- Record concomitant medications
- Record rescue medication use
- Collect study gel
- Collect e-diary

- Safety Visit Period 2 (±1 day). Procedures and assessments are as follows:
  - Vital signs
  - Physical examination
  - Skin examination / assessment at study gel site
  - [redacted]
  - [redacted]
  - Photographic evaluation of application site reactions, as needed (before study gel application)
  - Record AEs

- Record concomitant medications
- Record rescue medication use
- Apply study gel ([redacted] according to treatment assignment. Note: some study gel applications may occur outside the clinic visit.
- Dispense study gel (for out-patient portion)

- Day 9 to Day 22:
  - Out-patient portion Period 2: Subjects apply study gel according to their assigned treatment and record assessments as follows:
    - Apply study gel ([redacted] according to treatment assignment.
    - Photographic evaluation of application site reactions, as needed (before study gel application)
    - Record AEs
    - Record concomitant medications
    - Record rescue medication use
- Day 11 (±1 day):
  - Telephone Call Period 2 to assess safety and skin condition.
    - Record AEs
    - Record skin condition if applicable
    - Record concomitant medications
    - Record rescue medication use
- Day 15 (±1 day):
  - Follow-up Telephone Call Period 1 to assess safety and skin condition.
    - Record AEs
    - Record skin condition if applicable
    - Record concomitant medications
  - Safety Visit Period 2
    - Vital signs
    - Physical examination
    - Skin examination / assessment at study gel site
    - Photographic evaluation of application site reactions, as needed (before study gel application)
    - Record AEs
    - Record concomitant medications
    - Record rescue medication use

        - Apply study gel ([redacted] according to treatment assignment. Note: some study gel applications may occur outside the clinic visit.
        - Dispense study gel (for out-patient portion)

- Day 18 (±1 day):
    - Telephone Call Period 2 to assess safety and skin condition.
        - Record AEs
        - Record skin condition if applicable.
        - Record concomitant medications
        - Record rescue medication use

- Day 22 (+1 day):
    - EOS Visit Period 2: The visit procedures include safety assessments, and collection of study gel and e-diaries.
        - Vital signs
        - ECG
        - Pregnancy test (urine) (females only)
        - Clinical laboratory tests (hematology, serum chemistry, and urinalysis)
        - Physical examination
        - Skin examination / assessment at study gel site
        - Apply study gel at 6 am on Day 22
        - Photographic evaluation of application site reactions, as needed (before study gel application)
        - Record AEs
        - Record concomitant medications
        - Record rescue medication use
        - Collect study gel
        - Collect e-diary

- Day 29 (±1 day):
    - Follow-up Telephone Call Period 2 to assess safety and skin condition.
        - Record AEs
        - Record skin condition if applicable.
        - Record concomitant medications

The procedures and assessments to be performed at each visit are indicated in Table 2.

6.4 COMPLIANCE WITH THE PROTOCOL

The investigator must agree to implement the study protocol as written and adhere to the guidelines given in the "Investigator's Statement", which will be signed prior to the start of the study. The study will be performed in accordance with Health Insurance Portability and Accountability Act, Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, local laws, Food and Drug Administration (FDA) GCP regulations (21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312), and other applicable guidance documents.

If the investigator considers enrolling a subject that does not meet all inclusion or exclusion criteria, an exemption must be requested from the Kowa Research Institute, Inc. (KRI) Medical Monitor prior to subject enrollment. The justification for the exemption must be documented by the investigator. The approval or rejection of the exemption must be documented by the KRI Medical Monitor prior to the subject's enrollment or screen failure.

Protocol noncompliance must be reported to the Contract Research Organization [CRO] Medical Monitor and KRI. Each deviation and the reason for its occurrence must be documented and entered on the CRF/eCRF. KRI retains the right to require the withdrawal of any subject who violates the protocol.

6.5 TERMINATION OF THE STUDY

If, in the opinion of the investigator, the clinical observations in the study suggest that it may be unwise to continue, or if there is an unexpected, unacceptable or significant safety risk posed toward study subjects, the study may be terminated after consultation with the [redacted] and KRI. A written statement fully documenting the reason(s) for the termination will be provided to KRI. In addition, KRI may terminate the study at any time.

If it becomes apparent that subject enrollment is unsatisfactory with respect to quality or quantity, or data recording is inaccurate or incomplete on a chronic basis, or protocol requirements are not being met, KRI has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the investigator, the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities, if required. In the event of any serious or non-serious AEs having occurred at a site, all documentation relating to the event(s) must be obtained.

7.0 STUDY MEDICATION

7.1 DESCRIPTION OF STUDY MEDICATION

The study gels include K-285 and menthol gel.

- K-285 is a topical gel which contains [redacted]
- Menthol gel contains [redacted]

Each of the study gels contains the following excipients: [redacted]

7.2 DRUG PACKAGING

The study gels are filled in aluminum-laminated tubes at a weight of [redacted] of study gel per tube.

For each treatment arm, 2 types of kits containing study gel, dosing spoons, and application template materials will be prepared (for 1 week of dosing and 3 weeks of dosing) (Figure **2**).

[redacted]

Study gel

[redacted]

The blue color box in Figure **2** represents kits for subjects assigned to [redacted] (Period 1) (actual carton will be white). Each subject will apply [redacted] of assigned study gel [redacted]. The amount of study gel needed per subject is [redacted]). Each subject will be assigned a kit containing two [redacted]).

The pink color box in Figure **2** represents kits for subjects assigned to [redacted] (Period 1 and Period 2) (actual carton will be white). Each subject will apply [redacted]. The maximum amount of study gel needed per subject is [redacted]. Each subject will be assigned a kit containing [redacted]).

Dispensing of study gel is described in Section 7.5.1.

Replacement kits will be provided only if packaging is damaged prior to receipt of delivery.

7.3 DRUG LABELING

Study gel will be labeled with the following information:

1) Study number
2) Contents and amount
3) Lot number
4) Kit Number
5) The storage conditions

6) Name and address of Sponsor (e.g., KRI)
7) Caution - New Drug Limited by Federal Law to Investigational Use
8) Caution - Keep out of reach of children
9) Caution – Avoid open fire or smoking until the gel has dried
10) Instruction – Apply the gel using the provided dosing spoons according to the detailed instructions on the kit package label

7.4 DRUG STORAGE

Study gels must be stored at controlled room temperature of [redacted]) with excursions permitted between [redacted] as indicated on the drug label.

7.5 DISPENSING AND ADMINISTRATION OF TREATMENT

7.5.1 Dispensing of Study Gel

Study gel will be dispensed on Day 2, Day 8 and Day 15. A sufficient number of tubes to supply enough study gel for 1 week at a time will be provided.

7.5.2 Application Training

On Day -1, subjects will receive training on the application of study gel including video training. Further application instructions are provided in Appendix 15.3.

7.5.3 Drug Administration

[redacted]

[redacted]

[redacted]

[redacted]

7.5.4 e-Diary

An e-diary will be issued to each subject by study staff on Day 1 prior to randomization. Subjects will record pain intensity assessments (eVAS, Categorical Qualifying Pain Scale, Perceptible Pain Relief, and Meaningful Pain Relief), including dermal response (if applicable), rescue medications (if applicable) and study gel applications as detailed in the e-diary training. Documentation for the study leg and non-study leg (if required) will be performed at the time points specified in Table 2.

The actual time and date that each set of pain assessments is started at each time point must be recorded in the e-diary.

The e-diary will be collected from the subject on Day 8 (subjects dosing during Period 1) or Day 22 (subjects dosing during Period 2) after the EOS/ET assessment.

7.5.5 Physical Exercise

The standardized repetitive quadriceps muscle exercise is described in Section 5.3.4. Subjects will not engage in any strenuous physical activity during study period.

7.6 COMPLIANCE WITH PRESCRIBED STUDY GEL DOSING REGIMEN

The study gel will be applied at the clinic on Days 1 and 2. The study gel for application on Day 1 will be dispensed by the site pharmacy, and for Days 2-8 will be dispensed to the subjects prior to discharge on Day 2. For subjects assigned to Period 2, study gel for application by subjects will be dispensed at the Day 8 and Day 15 Safety visits. Study gel tubes will be weighed, in grams, and the total weight for all tubes recorded prior to dispensing to subjects. Study gel will be collected on Day 8 (for Period 1 subjects) and Day 22 (for Period 2 subjects), weighed and the final weight recorded. Compliance will be determined from the final weight of the tubes compared to the expected decrease from the starting weight, based on the assigned dosing schedule ([redacted] × the number of doses).

7.7 DRUG ACCOUNTABILITY

The investigator or designee will sign a receipt for the study gel when received. The study gel must be stored as described (Section 7.4), kept in a secured location to which only the investigator and designated staff have access, and dispensed only to those subjects formally enrolled in the study.

The investigator or designee must maintain an accurate record of the shipment and dispensing of study gel in a drug accountability ledger. Drug accountability will be monitored by the study monitor during monitoring visits and at the completion of the study. All drug will be inventoried by [redacted] at the conclusion of the study. Secure disposal at the end of the study will be arranged after the clinical study report has been finalized.

7.8 PROCEDURE FOR UNBLINDING

As needed, the randomization code may be broken by the investigator to manage an urgent medical event. When possible, unblinding will be reserved for situations where treatment allocation is required to be known for safety reasons. If possible, KRI and the [redacted] is contacted to discuss the case before the code is broken.

If it becomes necessary to unblind treatment information during the study, the reason for unblinding is documented in the CRF/eCRF. The investigator must contact KRI and the [redacted] promptly and explain the reason for the premature unblinding.

8.0 CONCOMITANT MEDICATION

The investigator must record the use of all concomitant medications including rescue medications, both prescribed and over-the-counter, in the CRF/eCRF. This includes drugs used on a chronic and as-needed basis. Subjects must be discouraged from starting any new medication, both prescribed and over-the-counter, without consulting the investigator, unless the new medication is required for emergency use.

8.1 GENERAL CONSIDERATIONS

All medications and other treatments taken by subjects within 30 days before dosing and during the study will be recorded in the CRF. Any changes in the concomitant medications after discharge from the clinic on Day 2, either prescribed or self-administered, will be documented and reviewed according to the schedule in Table 2.

8.2 PROHIBITED MEDICATION AND THERAPIES

The following medications and therapies are prohibited during the study:

- Oral or topical analgesic medications within 14 days before the Screening Visit.
- Systemic corticosteroid within 30 days before the Screening Visit.
- Prescription or over-the-counter products containing menthol or NSAIDs.
- Sleep medication, muscle relaxant, anticonvulsant, or antidepressant in the last 6 months to treat a chronic pain condition.
- Anticonvulsant or antidepressant for a non-painful condition at a dose that has not been stable for at least 3 months before the Screening Visit.
- The application or use of ice, heat, massage, and wrapping on the legs
- Medications or treatments that would significantly influence or exaggerate responses to the gel, or that would alter inflammatory or immune responses to the gel, within 30 days before the first dose of study gel (e.g., cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin vaccine, monoclonal antibodies, radiation therapy).
- Subjects will not engage in any strenuous physical activity during study period.

8.3 PERMITTED MEDICATION

Use of any rescue medication for DOMS is strongly discouraged until 168 hours after the first study gel application, at which time over-the-counter (OTC) acetaminophen (one 500 mg acetaminophen tablet twice daily, not more than every 6 hours) as rescue medication is permitted, if required. Subjects experiencing severe pain or inability to move or walk due to pain may be permitted to use rescue medication (one 500 mg OTC acetaminophen tablet twice daily, not more than every 6 hours) prior to 168 hours after the first study gel application. If subjects take rescue medication before the first 168 hours, it will be captured as a concomitant medication.

No other medications (including supplements) are permitted during the study, except as necessary to treat an AE, at the investigator's discretion.

9.0 ADVERSE EVENTS

9.1 ADVERSE EVENT DEFINITION

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the subject's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that subject.

Clinically meaningful (for a given subject) changes in physical examination findings and abnormal objective test findings (e.g. clinical laboratory tests [except for elevated test results for serum CK, Section 5.2.2.1], ECGs) are also recorded as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. test result is associated with accompanying symptoms, and/or;
2. test result requires additional diagnostic testing or medical/surgical intervention, and/or;
3. test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or;
4. test result leads to any of the outcomes included in the definition of a serious AE (SAE).

Merely repeating a test, in the absence of any of the above conditions, does not meet condition number 2 above for reporting as an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

A TEAE is defined as an AE that begins after the start of study gel or an event that begins before the start of the study gel and worsens in intensity after starting treatment.

9.2 REPORTING ADVERSE EVENTS

At each evaluation, the investigator will determine whether any AEs have occurred. The subject will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they will be recorded on the AE pages of the CRF or eCRF and in the subject's medical record. If known, the diagnosis will be recorded, in preference to the listing of individual signs and symptoms.

Adverse event reporting begins when informed consent is obtained and ends at the conclusion of the study, unless an unresolved AE is still being followed.

The severity of the AE will be graded as follows:

Mild	The AE is easily tolerated and does not interfere with normal daily activities.
Moderate	The AE causes some interference with daily activities.
Severe	The AE causes all normal daily activities to be completely halted.

The investigator will make a judgment regarding whether or not the AE was related to the study gel. (Please refer to the definitions below.) The investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to the study gel. However, even if the investigator feels there is no relationship to the study gel, the AE or laboratory abnormality **MUST** be recorded in the CRF/eCRF. The following guidance will be used by investigators when assessing relationship:

Related

- Occurs within a reasonable temporal sequence to administration of study gel or,
- Cannot be explained by concurrent disease or other drugs or chemicals or,
- Improves or disappears on stopping or reducing study gel (de-challenge)
- Reappears on repeated exposure to study gel (re-challenge)
- Is an unusual event that is known to be associated with the drug or this class of compound, and cannot be explained by other therapy or the participant's physical condition
- Unlikely to be attributed to concurrent disease or other drugs or a clinically reasonable response on withdrawal (de-challenge)

Unrelated

- Occurs with a temporal relationship to administration of study gel which makes a causal relationship improbable or,
- Other drugs, chemicals or underlying disease provide plausible explanations of causality or,
- Is known to be associated with the participant's clinical condition, or with other medication taken by the participant

The investigator will record the action taken and outcome for each AE according to the following:

Action taken

- None
- Treatment required
- Hospitalization
- Subject withdrawn
- Other (specify)

Action Taken With Study Treatment

- Dose not changed
- Drug interrupted
- Drug withdrawn
- Not applicable

Outcome

- Resolved: The event has recovered
  - Note: An SAE/AE stop date should be provided.
- Recovered/Resolved with sequelae: The study subject has recovered as much as may be expected but is left with sequelae of the event that are not expected to recover further
  - Note: If the sequelae are severe enough to represent a significant disability or incapacity then the event should be reported as an SAE.
- Recovering/Resolving: Can be used in cases where study subject is known to be clearly recovering from the event at the end of a study, although the event is not yet resolved, and the investigator and Medical Monitor agree that further follow-up is not necessary.
- Fatal: The study subject died as a result of the AE
  - Note: Death is considered an outcome of an AE rather than an AE in its own right, and the cause of death should be recorded as the AE. There may be rare circumstances where the cause of death is unknown and the death may have to be recorded as the event (e.g., "sudden cardiac death"). Adverse events resulting in death are SAEs.
- Not recovered/Not resolved: The subject has an AE that has not improved or recuperated at the time of the report

9.3 FOLLOW-UP OF ADVERSE EVENTS

If any AEs are present when a subject completes the study, or when a subject discontinues or is withdrawn from the study, the subject will be re-evaluated. At the investigator's discretion, minor AEs can be re-evaluated via telephone and documented. If the AE is still not resolved, additional follow-up will be performed as appropriate. Every effort will be made by the investigator or delegate to contact the subject until the AE is resolved or stabilized, or the Medical Monitor and investigator agree that further follow-up is not necessary. The follow-up of AEs will be documented in the subject's medical records.

10.0 SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Events that require expedited reporting will also be considered to be SAEs.

10.1 LIFE-THREATENING ADVERSE EVENT

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

10.2 HOSPITALIZATION

Hospitalization is defined as the subject being hospitalized overnight, or the subject's hospital stay being prolonged for at least an additional overnight stay. Pre-planned hospital stays or hospital stays for non-medical social reasons are not applicable. Twenty-three hour hospitalizations for observation will be discussed with the Medical Monitor to determine whether they are appropriate for SAE reporting.

10.3 IMPORTANT MEDICAL EVENT

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

10.4 PREGNANCY

Any subject who becomes pregnant during the study must immediately be discontinued/withdrawn. The investigator is required to notify the KRI Medical Monitor and [redacted] if any subject becomes pregnant during the study. Pregnant subjects will require periodic follow-up with documentation of the outcome of the pregnancy in the study records.

10.5 SUBJECT DISCONTINUATION AND WITHDRAWAL

If a subject experiences an AE that leads to discontinuation of study gel treatment and withdrawal from the study, the CRF/eCRF will identify the AE as the reason for withdrawal. Subjects that discontinue study gel treatment will be asked to continue scheduled study visits through the Follow-up phone call.

10.6 SERIOUS UNEXPECTED SUSPECTED ADVERSE REACTIONS

According to FDA CFR 312.32(a) and FDA Guidance "Safety Reporting Requirements for INDs and BA/BE Studies" finalized December 2012, *suspected adverse reaction* means any AE for which there is a reasonable possibility that the medicinal product caused the AE. The phrase "reasonable possibility" means there is evidence to suggest a causal relationship between the AE and the medicinal product.

The following are examples of types of evidence that would suggest a causal relationship between the drug and the AE (i.e., *reasonable possibility*):

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

Suspected adverse reactions are the subset of all AEs for which there is a reasonable possibility that the drug caused the event.

A suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or other applicable product information or is not listed at the specificity or severity that has been observed.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening AE, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any AE meeting the definitions of suspected adverse reaction, unexpected, and serious is considered a serious unexpected suspected adverse reaction (SUSAR). In accordance with the FDA Guidance "Safety Reporting Requirements for INDs and BA/BE Studies", finalized December 2012, KRI will unblind the study data for subjects experiencing SUSARs and only report those for subjects who are on study gel. All such reports will be submitted to the investigator(s), FDA, and IRB/IEC in an expedited manner.

10.7 SERIOUS ADVERSE EVENT REPORTING

SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY GEL, MUST BE REPORTED IMMEDIATELY TO THE STUDY MEDICAL MONITOR:

[redacted]

Sites needing to contact the Medical Monitor should use the above 24/7 SAE hotline number and [redacted] email before contacting an individual Medical Monitor. The hotline number will employ a call tree to contact individuals in order of a call list.

Lotus Clinical Research, LLC

[redacted]

Kowa Research Institute, Inc. will conduct a medical review of SAE reports.

Kowa Research Institute, Inc.

[redacted]

Kowa Research Institute, Inc. will obtain details from the investigator or CRO of all serious, unexpected and related AEs (or other events depending on the specific requirements) that should be reported to IRBs/IECs, as appropriate. Written confirmation that these serious, unexpected and related AEs have been submitted to the IRB/IEC must be forwarded to KRI and kept in the investigator files.

11.0 STATISTICAL METHODS AND DATA ANALYSIS

In general, assessments with continuous outcomes will be summarized using the descriptive statistics n, mean, standard deviation (SD), median, minimum and maximum. For assessments with categorical outcomes, frequency counts and percentage will be calculated. Detailed statistical methodology will be presented in a separate statistical analysis plan.

11.1 SAMPLE SIZE JUSTIFICATION

The parameters are conservatively estimated based on the DOMS study with [redacted] gel. The between-group difference in the mean [redacted] is 11.07 with a SD of 25.62. To have statistical power of 90%, [redacted] Taking into account information loss caused by missing data, it is estimated that [redacted] need to be treated with each study gel.

11.2 STUDY POPULATIONS

Three analysis populations will be evaluated:

- The full analysis set (FAS) will include all randomized subjects who have a baseline pain score and at least 1 study gel applied.
- The per-protocol set (PPS) will include all randomized subjects who have a baseline pain score, at least 1 study gel applied, and no major protocol violations.
- The safety set will include all subjects who have at least 1 study gel applied.

11.3 DISPOSITION

The number of subjects screened, randomized, and treated will be summarized. The number of subjects discontinuing treatment/withdrawing from the study will be summarized along with the reasons for discontinuation/withdrawal. Subjects who are screen failures along with the main reasons for failure will also be summarized.

11.4 DEMOGRAPHIC/BASELINE INFORMATION

Demographics and other baseline characteristics will be summarized with descriptive statistics. For quantitative data, means, medians, standard deviations, minimum and maximum values will be determined. For qualitative data, percentages will be calculated.

11.5 ANALYSIS OF EFFICACY PARAMETERS

11.5.1 Primary Efficacy Parameters

The primary analysis population is the FAS. The primary analysis will be repeated using the PPS. [redacted]

If there exist missing VAS values to be imputed, any such values will be imputed before calculating the [redacted]. Intermediate missing VAS values due to an omission of recording pain intensity or subject's sleep will not be imputed, therefore, the observed values before and after the missing measurement will be directly connected in order to calculate the [redacted] If subjects need to take the rescue medication, they will record their pain intensity in the e diary before taking the rescue medication. If the rescue medication is taken within 6 hours of a nominal pain intensity assessment time point, the pain intensity score that was recorded before taking the rescue medication will be carried forward to the next pain intensity assessment time point. Missing values caused by withdrawal from the study due to events which are not preferable to subjects such as an adverse event and/or lack of efficacy will be imputed by last observation carried forward (LOCF) while those values due to lost to follow-up will be imputed under the missing at random (MAR) assumption with the multiple imputation (MI) technique. By using the MI technique, 100 datasets will be generated. After calculating the [redacted] an analysis of covariance (ANCOVA) model will be applied for the primary endpoint with gender and treatment as main effects and baseline pain as a covariate in each dataset. Multiple results will be combined using Rubin's rule. As for a sensitivity analysis, the LOCF values will be replaced by the worst value observed in this study, and then the same procedure will be applied.

11.5.2 **Secondary Efficacy Parameters**

A mixed effect model repeated-measures (MMRM) will be applied to the PID while standing and PID at rest to investigate treatment differences. [redacted]. The time to first dose of rescue medication, will be analyzed using the Kaplan-Meier method to estimate the survival distribution function.

11.6 ANALYSIS OF SAFETY DATA

The safety endpoint data will be summarized for the safety set.

The AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). A general summary of the AEs and SAEs will be summarized by overall number of AEs, severity and relationship to study gel, per treatment group. The number of AEs leading to discontinuation/withdrawal and SAEs leading to death will also be summarized. The incidence of AEs will be summarized by body system and treatment group. The incidence of TEAEs will also be summarized by system organ class and preferred term.

The clinical laboratory data will be summarized by treatment group, along with changes from the baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values, which are identified as being clinically significant, will be flagged.

Vital signs will also be summarized by treatment group and time point, along with the changes from baseline.

All AE, clinical laboratory, vital sign, physical examination, study gel application site reaction, study gel use and concomitant medication use will be presented in data listings.

[redacted]

12.0 STUDY MANAGEMENT AND DATA COLLECTION

12.1 ETHICAL CONDUCT OF THE TRIAL

This study will be conducted according to the protocol, FDA GCP, as described in 21 CFR Parts 11, 50, 54, 56, and 312; the World Medical Association Declaration of Helsinki; the Health Insurance Portability and Accountability Act (HIPAA); and ICH GCP (E6/R1). Each investigator will conduct the trial also according to applicable local or regional regulatory requirements.

12.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The IRB/IEC must be constituted according to the applicable state, federal and local requirements of each participating location, and those of the ICH GCP guidance and FDA GCP regulations.

It is the responsibility of each investigational site to submit the protocol, Investigator's Brochure, subject informed consent, subject recruitment materials (if applicable), and other required documentation to the IRB/IEC for review and approval. Copies of the written approvals must be provided to [redacted] The documentation should clearly mention the approval/favorable opinion of the protocol, the subject ICF, and subject recruitment materials (if applicable). The respective version dates are to be included. The written approvals and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRB/IEC and provided to [redacted] prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB/IEC has direct participation in the study, written notification regarding his or her abstinence from voting must also be obtained.

Sites must adhere to all requirements stipulated by the IRB/IEC. This includes notification to the IRB/IEC regarding protocol amendments; updates to the subject informed consent and recruitment materials intended for viewing by subjects; Investigational New Drug safety reports; serious and unexpected AEs; updates regarding the ongoing review of the study at intervals specified by the IRB/IEC; and final study reports or summaries.

It is the responsibility of each investigational site to submit information to the appropriate IRB/IEC for annual review and annual re-approval.

12.3 SUBJECT INFORMED CONSENT

Prior the implementation of study procedures, subjects and persons conducting the consent discussion will be required to sign and date the IRB/IEC-approved ICF and each subject will be given a copy. In addition, this information will be recorded in the subject's medical record (i.e., source document).

The written consent document will embody the elements of informed consent as described in the HIPAA, World Medical Association Declaration of Helsinki, FDA 21 CFR Part 50.25, ICH GCP, and in accordance with any local regulations. The investigator is responsible for the preparation, content, and IRB/IEC approval of the ICF. The ICF must

be approved by the site-designated IRB/IEC and be acceptable to KRI and [redacted].

The ICF must be written in a language fully comprehensible to the prospective subject. The investigator or designee will give the subject adequate opportunity to read it before it is signed and dated. Information provided will be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB/IEC. Subjects must be given ample opportunity to inquire about study details.

12.4 AMENDMENTS TO THE PROTOCOL

An amendment must be agreed to in writing by KRI and [redacted], submitted as an Investigational New Drug (IND) application amendment, and submitted to and approved by the respective IRB/IEC for each investigational site before it is implemented. Written approval of a protocol amendment is not required prior to implementation for changes to the protocol, which eliminate immediate hazard to the subject; however, approval must be obtained as soon as possible thereafter. Approved amendments must also be signed by the investigator.

12.5 STUDY INITIATION

The investigator must not enroll any subjects prior to the completion of a formal meeting conducted by a representative of [redacted] (or KRI). This meeting will include a detailed review of the study protocol and CRF/eCRFs. Study gel will not be supplied to an investigator until all the necessary pre-study requirements have been completed and essential signed documents are received by [redacted], as applicable, and KRI.

12.6 STUDY MONITORING

It is the responsibility of the investigator to ensure that the study is conducted in accordance with the protocol, ICH/FDA GCPs, applicable regulatory requirements, HIPAA, and the current Declaration of Helsinki. Valid data are to be entered into the CRFs/eCRFs. Monitoring activities will be conducted as described in an approved Monitoring Plan. Oversight visits may be conducted by KRI Clinical Operations to assess monitoring performance.

To achieve this objective, the monitor's duties are to aid the investigator and, at the same time, KRI in the maintenance of accurate, complete, legible, well-organized and easily retrievable data. The monitor will review the protocol with the investigator. In addition, the monitor will explain the investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study gel.

The investigator will permit the representatives of KRI and [redacted] to monitor and oversee the study as frequently as [redacted] (or KRI) deems is necessary to determine that data recording and protocol adherence are acceptable. The CRFs/eCRFs and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant Standard Operating Procedures (SOPs), ICH GCP guidance, and FDA GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to

confirm information contained in the CRFs, such as past medical history and secondary diagnoses. The investigator and staff will be expected to cooperate with the monitor/KRI and provide any missing information, whenever possible.

All monitoring and KRI oversight activities will be reported and archived. Any issues identified will be reported and followed-up until resolved. In addition, each monitoring visit will be identified at the investigational site by the monitor's / KRI's signature and date on the study-specific monitoring log.

12.7 CASE REPORT FORM

All subject data generated during the study will be recorded on the CRF/eCRF.

The investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the CRFs/eCRFs, designed specifically for this study and supplied by [redacted] for each subject.

[redacted] will only consider the CRFs/eCRFs to be complete after they are reviewed and signed by the investigator, indicating his/her assurance of the accuracy of all recorded data. It is expected that the investigator and staff will cooperate with the monitoring team and provide missing data in a timely manner.

12.8 VERIFICATION PROCEDURES

In fulfillment of their obligations to KRI and to verify compliance with this protocol, ICH GCP guidance, and FDA GCP regulations, the investigator will permit [redacted], the IRBs/IECs, the monitor, and regulatory authorities to have direct access to the subject's medical records.

It is the investigator's obligation to ensure documentation of all relevant data in the subject's medical record, CRFs/eCRFs, and on study forms, when applicable, according to procedures provided in the protocol.

The investigator will maintain a Subject Identification Code List to enable unambiguous identification of the subjects (subject names and corresponding subject numbers). The Subject Identification Code List is an essential document and as such must be maintained according to the ICH GCP guidelines.

12.9 RETENTION OF RECORDS

All documentation pertaining to the study will be retained by KRI and [redacted] in accordance with U.S. FDA regulations and the ICH GCP guidance document.

[redacted] will provide each investigator with a study binder, which will be used to file the Investigator's Brochure; protocol; drug accountability records; correspondence with the IRB/IEC, KRI, and [redacted]; and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all

CRFs/eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities and KRI or its designees.

The investigator and [redacted] will retain records required to be maintained under federal regulations for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, these documents will be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by KRI. In addition, the investigator must make provision for the subject's medical records to be kept for the same period of time.

Subjects' medical records and other original data will be archived in accordance with applicable regulations and requirements established by the investigational sites.

12.10 INSURANCE AND INDEMNITY

KRI's obligations regarding insurance and indemnification are described in other documents or agreements.

12.11 AUDIT

It is the responsibility of [redacted] and KRI to perform audits (if applicable), as part of implementing quality assurance. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, SOPs, ICH/FDA GCPs, HIPAA, and other applicable regulatory requirements. The auditor and regulatory authorities will require direct access to the subject's medical records and all study records.

13.0 USE OF INFORMATION

13.1 GENERAL ASPECTS

All information concerning [redacted] and KRI, such as patent applications, formula, manufacturing processes, basic scientific data or formulation information supplied by KRI and not previously published, are considered confidential and will remain the sole property of KRI. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of KRI, except for official representatives, such as regulatory authorities.

It is understood by the investigator that the information developed in this clinical study, in connection with the development of K-285 will be used by KRI and, therefore, may be disclosed by KRI as required to other clinical investigators, other pharmaceutical companies and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to KRI complete test results and all data compiled in this study.

13.2 SUBJECT CONFIDENTIALITY AND DATA PROTECTION

Kowa Research Institute, Inc. and its designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be linked to the CRF/eCRF via a unique identification number and the subject's initials. *The data will be blinded correspondingly in all data analyses*.

However, in compliance with the guidelines and regulations of the US FDA concerning the acceptance of clinical studies in support of IND applications and the ICH GCP (whether performed in the United States or elsewhere), and in fulfillment of its obligations to KRI to verify compliance with this protocol, KRI's designee requires that the investigator to permit its monitor, representatives from the FDA, KRI's designated auditors, IRBs/IECs, and other governmental regulatory authorities to review the subject's primary medical records (source data or documents) including, but not limited to laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports related to deaths occurring during the study.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the investigator will obtain such permission in writing from the subject before the subject is entered into the study.

13.3 FINAL REPORT AND PUBLICATION POLICY

All information regarding this study will be kept strictly confidential. All data derived from the study will be the property of KRI. The investigator must undertake not to submit any part of the data from this study for publication without prior consent of KRI. KRI may disclose data derived from the study to other investigators and drug regulatory authorities.

After completion of the study, and as agreed by the investigator and KRI, the investigator may send a draft manuscript to KRI to be reviewed in order to reach an agreement regarding publication. The investigator must receive written approval from KRI before the final version of the manuscript is submitted for publication.

At the conclusion of the study, after the data are analyzed, KRI or its designee will prepare a final clinical report.

14.0 REFERENCES

1. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin N Am 1996, 6:489-504.
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3. Jüni P. Are selective COX 2 inhibitors superior to traditional nonsteroidal antiinflammatory drugs? BMJ. 2002 June 1; 324(7349): 1287–1288.
4. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. BMC Fam Pract. 2004 May 17;5:10.
5. Oz M., El Nebrisi E.G., Yang, K-H.S., Howarth F.C, and Al Kury LT. Cellular and Molecular Targets of Menthol Actions. Front. Pharmacol. 2017; 8:472.
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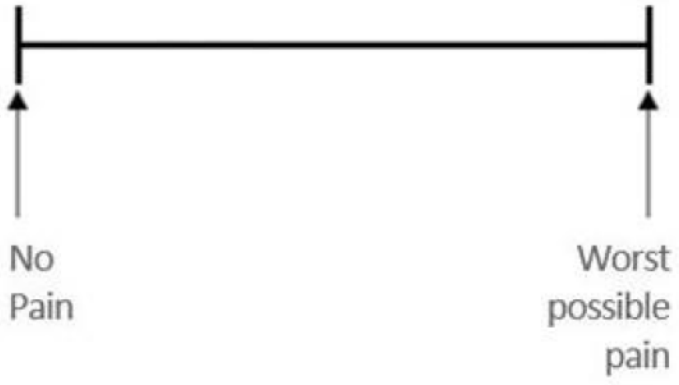
15.0 APPENDICES

15.1 APPENDIX 1

VISUAL ANALOG SCALE (EXAMPLE OF PAPER VAS)

Assessment of the pain intensity at rest and while standing using a paper pain VAS.

Please record the pain intensity while **at rest/while standing** in the **dominant/non-dominant leg** that you are experiencing right now:

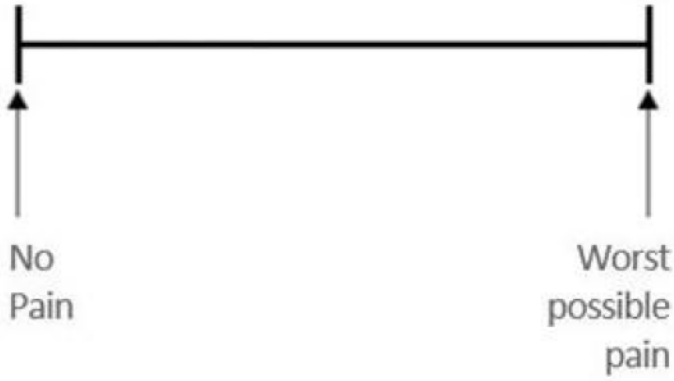


Schematic is a representation of the paper VAS image that will be presented to subjects.

VISUAL ANALOG SCALE (EXAMPLE OF ELECTRONIC VAS)

Assessment of the pain intensity of DOMS at rest and while standing using a pain eVAS.

Please record the pain intensity while **at rest/while standing** in the **study leg/non-study leg** that you are experiencing right now due to DOMS (delayed onset muscle soreness):



Schematic is a representation of the eVAS image that will be presented to subjects.

15.2 APPENDIX 2

[redacted]

[redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

[redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

15.3 APPENDIX 3

[redacted]

[redacted]

[redacted]

[redacted]

15.4 APPENDIX 4

[redacted]

[redacted]

[redacted]

[redacted]