[redacted]

STATISTICAL ANALYSIS PLAN

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

Protocol Version 2.0 (28MAY2020)

ClinicalTrials.gov NCT04484428

SPONSORED BY

Kowa Research Institute, Inc

[redacted]

PREPARED BY

[redacted]

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
V1.0	13APR2021	Initial Version

APPROVALS

[redacted]

Author:

16-Apr-21

Date

Reviewed:

15-Apr-21

Date

Approved:

15-Apr-21

Date

Approved:

15-Apr-21

Date

Approved:

15-Apr-21

Date

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LIST OF ABBREVIATIONS

AE	Adverse event
API	active pharmaceutical ingredients
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CFR	Code of Federal Regulations
CRF	case report/record form
CRO	Contract Research Organization
DOMS	delayed onset muscle soreness
ECG	electrocardiogram
EOS	End of Study
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
LOCF	last observation carried forward
LOE	lack of efficacy
OTC	Over the counter
PPS	per protocol set

1 PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number K-285-201, Version 2.0 (May 28th, 2020) from Kowa Research Institute Inc. The SAP contains detailed information to guide the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR).

This SAP is being written with due consideration of the recommendations outlined in the most recent International Council on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the ICH E9 (R1) Addendum, the most recent ICH E3 Guideline and the Guidance for Industry: Structure and Content of Clinical Study, and the most recent FDA draft Guidance for Industry – Analgesic Indications: Developing Drug and Biological Products, dated February 2014.

This SAP describes the data sets that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified as *post hoc* in the CSR.

2 PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 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 delayed onset muscle soreness (DOMS).

2.1.2 Secondary Objectives

Secondary objectives of this study are to determine:

- 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

2.2 Overall Study Design and Plan

2.2.1 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, 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 untimed 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] 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: [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. Due to unexpected problems that occurred after 20 subjects randomized, the e-diary vendor was switched from ERT to [redacted]. Newly enrolled subjects will utilize the [redacted] e-diary system. 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).

[redacted]

2.2.2 Study 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/m2, inclusive.

2.2.3 Treatment Regimens

A description of each regimen is provided below:

- K-285:
- Menthol gel:

2.2.4 Treatment Group Assignments or 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.

Subjects will be assigned to study treatment via appropriate randomization methods, in accordance with the randomization schedule generated by the allocation vendor ( ), prior to the start of the study, using validated internal software. Once a

randomization number has been assigned to a subject, it must not be re-assigned to a different subject.

[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). 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.

2.2.5 Sample Size Determination

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 120 subjects need to be treated with each study gel.

2.2.6 Interim Analysis for Futility Assessment

[redacted]. The interim analysis will assess the futility of the trial (conditional power <0.05) based on efficacy of K-285 to menthol gel using the FAS. That is, if the conditional power is less than 0.05 (i.e., < 5%), the study would have met the stopping rule/decision criteria to stop for futility. The conditional power will be calculated under the assumption that the effect size estimate at the interim analysis is true. See Section 11 of SAP for more details.

An independent team of biostatisticians and statistical programmers will perform the interim analysis within a folder that has restricted access to only the independent team members to maintain the blinding of the study.

Interim analysis was conducted using 120 randomized subject data on Feb 26, 2021. The study has met the stopping rule to stop for futility because the conditional power is less than 0.05. As a result, 126 subjects randomized before the interim analysis will be included in final analysis, rather than the planned 240 subjects.

3 GENERAL ANALYSIS AND REPORTING CONVENTIONS FOR ANALYSES

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies are provided in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies

All continuous study assessments will be summarized overall and by time point (as applicable) using the descriptive statistics n, mean, SD, median, and range (minimum, and maximum). All of the categorical study assessments will be summarized overall and by time point (as applicable)

using frequency counts and rates of occurrence (%). Changes from baseline for continuous outcomes will be presented as their corresponding continuous measures for post-baseline visits. All study data will be listed by subject, and time point (as applicable).

No preliminary rounding will be performed; rounding will only occur after the analysis. To round, consider the digit to the right of the last significant digit: if <5, then round down; if ≥5, then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. A percentage of 100% will be reported as 100%. Minimums and maximums will be presented with the same precision as the original data.

All analyses will be performed using the SAS System® version 9.4 or higher. The domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, figures, and listings. The submission ready SDTM and ADaM datasets will be provided to the sponsor along with display deliveries.

The following conventions will be used throughout the study analysis:

- Time T0 is the time of first treatment (first gel application) with study drug.
- The date of first treatment with study drug is Day 1.
- Assessment visit times are defined by time of treatment administration.
- Baseline value is defined as the last valid measurement prior to the dosing of study treatment.
- The change from baseline will be calculated as post-baseline value minus baseline value. If either the baseline or post baseline value is missing, the change from baseline is set to missing as well.
- Pain intensity difference (PID) is to be calculated by subtracting the pain intensity at each time point from the pain intensity at time 0
  $\mathbf{PID_t = PI_t - PI_0}$
- The number of days in the study is computed as: [Date of study completion or withdrawal minus the date of first study drug administration] + 1.

4 STUDY ASSESSMENTS

4.1 Efficacy Evaluations

4.1.1 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 (see Table 2 of Protocol). 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).

4.1.2 Visual Analogue 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 (see Appendix 1 of Protocol).

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 (see Appendix 1 of Protocol).

4.1.3 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 of Protocol.

4.1.4 Rescue Medication Use

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 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.

4.2 Safety Evaluations

Following safety evaluations will be performed. Refer section 9 of this SAP.

- Treatment emergent adverse event (TEAE) reports,
- Laboratory test results,
- Vital signs,
- Physical examinations,
- ECG findings
- Skin Examination (Study gel application site reaction)
- Residue Evaluation

5 SUBJECT SUMMARIES

5.1 Analysis Populations

Analysis populations are defined as follows:

- Full Analysis Set (FAS) will include all randomized subjects who have a baseline pain score and at least 1 study gel applied. Subjects will be analyzed according to the treatment they are randomized to.
- 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. Subjects will be analyzed by treatment group according to the actual treatment received, i.e., “as treated”.
- Safety set will include all subjects who have at least 1 study gel applied. Subjects will be analyzed by treatment group according to the actual treatment received, i.e., “as treated”.

Analysis populations will be determined before final data base lock and study unblinding.

The primary and secondary efficacy analyses will be performed using FAS population. Efficacy analyses will also be carried out using PPS populations for selected endpoints as appropriate. Baseline characteristics will be summarized using FAS population and safety endpoints will be summarized using Safety population. All baseline characteristics and safety summaries will be presented by Treatment Arm and/or by Treatment assignment as specified below.

- Treatment Arm
  - K-285
  - Menthol
- Treatment Assignment
  - K-285 1-week [redacted] (K-285 1w)
  - K-285 3-week [redacted] (K-285 3w [redacted])

- K-285 3-week [redacted] (K-285 3w [redacted])
- Menthol 1- week [redacted] (Menthol 1w)
- Menthol 3-week [redacted] (Menthol 3w [redacted]
- Menthol 3-week [redacted] (Menthol 3w [redacted])

5.2 Disposition of Subjects

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 inclusion/exclusion criteria and post-exercise inclusion criteria violation will also be summarized.

A listing of randomized and subject disposition will also be produced.

5.3 Protocol Deviations

Protocol deviations will be summarized, and all protocol deviations will be listed.

6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics and Baseline Characteristics

Demographic variables include age, sex, race, and ethnicity. Baseline characteristics include height, weight (kg), and body mass index (BMI; kg/m2). Demographics and baseline characteristics including identification of the study leg and baseline pain intensity of the study leg will be presented in a by-subject listing and summarized overall and by treatment group using FAS population.

For quantitative data, means, medians, standard deviations, minimum and maximum values will be determined. For qualitative data, counts and percentages will be calculated.

6.2 Medical History

Medical history including 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.), as collected at screening, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and summarized by system organ class (SOC) and preferred term (PT) in a frequency table based on the safety population. The SOC and PT will each be sorted in descending order by overall frequency. Medical histories will also be presented in a by-subject listing using the coded and verbatim history terms.

AEs that occur prior to treatment or that are related to a medical history event will be captured as medical history prior to database lock.

6.3 Concomitant Medication

All medications and other treatments taken by subjects within 30 days before dosing and during the study will be recorded in the eCRF. Any medication/therapy that stops at or after the date and

time of start of treatment or those with missing stop dates are considered concomitant medication/therapy.

Concomitant medications will be coded using the March 1, 2018 version of the WHODrug. Subjects who take concomitant medications will be presented in a by-subject listing of verbatim and coded terms and summarized by drug class and preferred name, overall and by treatment group, for the safety population.

A by-subject listing of all concomitant medications will be presented. Additionally, a summary and by-subject listing of concomitant medications that were prescribed or modified at or after the time of discharge on study day will also be presented.

7 STUDY DRUG EXPOSURE

Gel application information is captured on eDiary. Subjects who miss the previous gel application entry (and only the previous one) will be allowed to enter the missed gel application when they login in prior to the next scheduled gel application diary. Since the actual gel application time for the missing gel application will not be captured at the next entry, the date/time for the missing gel application will be imputed with the previous scheduled gel application time. Details of each gel application will be displayed in data listings.

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 (2.8 grams per dose × the number of doses).

The compliance will be measured by the ratio between actual weight decreased and the expected decrease from starting weight of a study gel tube. It will be summarized in a table by treatment group as well as displayed in a data listing for the safety population.

8 EFFICACY EVALUATION

8.1 Efficacy Endpoints

8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the sum of PID between 0 (baseline) to 24 hours ([redacted]) for the study leg after the first study gel application while standing using a 0-100 point eVAS.

8.2 Handling of Dropouts or Missing data

Missing VAS values up to 168 hours caused by early withdrawal from the study due to events which are not preferable to subjects such as an adverse event (AE) and/or lack of efficacy (LOE) will be imputed by last observation carried forward (LOCF).

If missing VAS values caused by withdrawal other than AE and/or LOE will be imputed for each treatment group separately under the missing at random (MAR) assumption with the multiple imputation (MI) technique. The imputation will be carried out in SAS version 9.4 or later, using the full conditional specification method (FCS) with a regression model approach (Carpenter and Kenward, 2013). By using the MI technique, 100 datasets will be generated. After calculating the SPID, an analysis of covariance (ANCOVA) model will be applied for the primary endpoint with gender and treatment as fixed effects and baseline pain as a covariate in each dataset. Multiple results will be combined using Rubin's rule (Little and Rubin, 1987), and will be done in SAS using PROC MIANALYZE. A significance test of the treatment difference at the two-sided 0.05 level and corresponding 95% confidence intervals will be calculated. However, the multiple imputation is used only for subjects that have a baseline.

If there exist missing VAS values to be imputed, any such values will be imputed before calculating the SPID. 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 SPID. If subjects need to take the rescue medication, they will record their pain intensity in the eDiary 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.

8.2.1 Assessment Time Windows

Data are generally reported according to the nominal time of clinic visits and assessments as specified in the protocol. Refer Section 2.2.1 of this SAP (study design) for time windows for different assessments.

8.3 Analysis Method for the Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the sum of PID between [redacted] ([redacted]) for the study leg after the first study gel application while standing using a 0-100 point eVAS. The primary analysis of the primary endpoint will be based on the FAS.

[redacted]

The durations between nominal time points will be calculated using the actual times of the pain score measurement. If the actual time is missing the nominal planned time will be used.

The primary endpoint will be analyzed using an ANCOVA model, which will include treatment and gender as fixed effects and baseline eVAS score as a covariate. The least square (LS) mean, standard error (SE) and associated 95% confidence interval (CI) for each treatment group will be estimated. In addition, the LS mean difference between each treatment group, SE, p-value and the associated 95% CI will also be computed. Descriptive summaries (including mean, SD, median, minimum, and maximum) will also be presented. Missing data imputation methodology is described in Section 8.2 in this SAP.

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. A nonparametric test may be conducted if the normality assumption is violated. An ANCOVA with unequal variances may be conducted if the constant variance assumption is violated.

To explore the impact of collecting e-diary data from different vendors, a sensitivity analysis by including both baseline eVAS score and the e-diary vendor in the model will be performed. Since majority of the eVAS data are collected by the second vendor, an analysis based on the second vendor's data only will be performed also.

8.4 Analysis Method for the Secondary Efficacy Endpoints

SPID Outcomes

For non-study leg, [redacted] after the first study gel application while standing using a 0-100 point eVAS, will be calculated, summarized, and analyzed similarly to primary endpoint.

The following secondary efficacy SPID outcomes are calculated and analyzed similarly to primary endpoint of sum of PID between [redacted] for the study leg after the first study gel application while standing using a 0-100 point eVAS, adjusting for the respective time periods:

- 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

Change from Baseline in PID

The Mean change from Baseline in pain intensity difference (PID) while standing and rest at different time points, after the first study gel application using a 0-100 point eVAS, will be summarized descriptively.

Time-specific mean change from baseline in PID will be assessed using a mixed model repeated measures (MMRM) with PID as the dependent variable. Fixed effects of the model include treatment arm, time, the treatment arm by time interaction, baseline eVAS, and gender. Subject is a random effect. A completely general (unstructured) covariance matrix will be used. A first-order autoregressive covariance matrix will be used if the model with an unstructured covariance matrix does not converge. Pairwise comparisons at each time point will be determined from the MMRM, and model-based means (LS means) and standard errors will be plotted for visual comparison of the treatment group outcomes. Only scheduled measurements will be included in the MMRM.

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. 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.

Both time to perceptible and meaningful pain relief will be analyzed using Kaplan-Meier curves with the log-rank test. Subjects will be censored at the time of safety visit on Day 8 or at the time of dropout. Estimated median time to perceptible/meaningful pain relief as well as their 95% confidence intervals will be tabulated by treatment group along with the number and percent of subjects censored.

The proportion of subjects with perceptible pain relief and meaningful pain relief at rest and while standing, both at, between [redacted], will be summarized descriptively by treatment group, using counts and percentages, along with 95% confidence intervals and CMH chi-square or Fisher exact *p*-values. This will also be analyzed using logistic regression model with treatment as an explanatory variable with gender and baseline eVAS (<median, >=median) as covariates. For treatment comparison, the odds ratio, 95 % CI and p-value will be presented.

Rescue Medication Usage

The proportion of subjects receiving rescue medication will be summarized descriptively by treatment group, using counts and percentages, along with 95% confidence intervals and CMH chi-square or Fisher exact *p*-values.

Time to first administration of rescue medication is the date/time of the earliest rescue medication use minus the date/time of administration of study drug. If the subject receives no rescue medication, then the value will be censored at 168 hours or at dropout.

Time to rescue medication will be analyzed using Kaplan-Meier curves with the log-rank test. Estimated median time to first use of rescue as well as its 95% confidence interval will be tabulated by treatment group along with the number and percent of subjects censored.

Total (mg) rescue medication used will be summarized descriptively. For each summary period [redacted], the mean number of rescue medication per day and the percentage of rescue-free days will be calculated. For each period and overall, cumulative rescue medication use will be displayed. Any data recorded after 168 hours, will not be included in any summaries.

8.5 Other Exploratory Analyses

SPID0-24, SPID0-48, SPID0-72, [redacted] at rest and while standing will be compared between study leg and non-study leg conditional on each of treatment groups based on a mixed model. The model will include treatment, type of leg, treatment by type of leg interaction, and gender as fixed effects and baseline eVAS score as a covariate. A compound symmetry covariance structure will be used to account for correlation between study leg and non-study leg within same subject. The LS mean difference between study leg and non-study leg, SE, p-value and the associated 95% CI will be computed for each of the treatment group.

If any other exploratory analyses or any subgroup analyses are performed after the SAP finalized, they will be documented in Clinical Study Report (CSR).

9 SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

All safety outcomes will be summarized using the safety population. Safety outcomes include:

- Incidence of treatment-emergent AEs (TEAEs)
- Changes from baseline in clinical laboratory test results
- Changes from baseline in vital sign measurements
- Changes from baseline in physical examinations
- Changes from baseline in ECG findings
- Skin Examination (Study gel application site reaction)
- Residue Evaluation

9.2 Adverse Events

Treatment-emergent AE 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. Verbatim terms used by investigators to identify AEs in the CRFs will be mapped to the appropriate preferred (PT) and system organ class (SOC) using a standardized coding dictionary (MedDRA Version 21.0 or higher). All coding will be reviewed prior to database lock. All recorded AEs/SAEs and TEAEs will be summarized and listed for each treatment group.

In addition to a listing of all TEAEs, separate listings of subjects with SAEs and listings of subjects with severe, treatment related, and AEs leading to premature discontinuation will be provided.

An overall summary will be produced for each treatment group of both the number of events and the number of subjects with TEAEs, SAEs, TEAEs by severity, TEAEs by relationship to treatment, and TEAEs leading to premature discontinuation.

The incidence of TEAEs will be summarized for each treatment group by SOC and PT within SOC (sorted in descending order by overall frequency). These summaries will be given in separate tables for the following categories of TEAEs:

- All TEAEs
- TEAEs leading to premature discontinuation
- SAEs

Also summarized will be TEAEs by maximum severity and by maximum relatedness to treatment. Adverse events will be deemed treatment related if they were recorded as probably, possibly, or definitely related.

If a given subject experiences a TEAE that maps to the same PT more than once, the subject will be counted once for the PT at its greatest severity (i.e., mild, moderate, or severe) and causality (i.e., attribution to study medication).

Duration of an AE will be computed in days (or in hours when duration of the AE is less than 1 day) as the stop date/time of the event minus the start date/time plus 1. If reported as ongoing at the time of database lock, the stop date/time is defined as the date/time of the last visit or the last date/time of any AE for the subject in the database, whichever is later. If an AE is considered resolved, but the stop date is missing, the last day of the month will be imputed if the month and year are available. If only the year is available, and the year is the same as the year of the last visit, the stop date will be the latest of the last visit date or latest AE for the subject in the database. If the year of the AE is prior to the year of the last treatment, the end day and month will be set to 31 December.

For missing or partial start dates, it is most conservative to impute them as temporally related to the first dose of study medication. The following chart will be used to impute start date:

Missing Portion	*Prior to Treatment*	*Same as Treatment Start Date*	*After Treatment Start Date*
Day	Month and Year < Month and Year of first treatment: Start Day = first day of the month Stop Day = last day of the month	*Month and Year = Month and Year of first treatment:* Start Day = Day of first treatment Stop Day= last day of the month	*Month and Year > Month and Year of First Treatment:* Start Day = first day of the month Stop Day= last day of the month
Day and Month Define Day as above, then:	*Year < Year of first treatment:* Start Month = July Stop Month = Dec	*Year = Year of first treatment:* Start Month = Month of first treatment Stop Month = Dec	*Year > Year of first treatment:* Month = January Stop Month = Dec
Day, Month, and Year	To be conservative, completely missing start dates will be set to the date of first treatment, completely missing end dates will be set to the date of last contact.		
Time	Missing start times will be imputed as 00:01 (or the start time of the first dose administration if AE occurred on the date of first dose administration) Missing stop times will be imputed as 23:59		

After following these imputation rules, if the start date is imputed as a date after the end date, the start date will be set to the end date to provide a positive duration for the AE.

Missing assessments for AE study medication relationship, or severity will be analyzed as related, severe, and associated, respectively. No other imputation is planned for safety data unless otherwise specified below

9.3 Deaths, Serious Adverse events, and Other Significant Adverse Events

A serious adverse event (SAE) is defined as an event that may constitute a significant medical

hazard or side effect, regardless of the investigator or sponsor's opinion about its relationship to study material. Serious events include, but may not be limited to, any event that:

- Is fatal
- Is life-threatening (places the subject at immediate risk of death while the event is occurring)
- Requires inpatient hospitalization or prolongs hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event

Significant untoward medical events that may not be life-threatening or result in death or hospitalization, or events that require intervention to prevent one of the outcomes listed above or that result in urgent investigation, may be considered serious. Elective hospitalizations for conditions that existed before administration of study material are not to be considered SAEs. Serious adverse events and deaths will be listed and summarized separately for the safety population.

9.4 Clinical Laboratory Evaluation

Clinical laboratory samples will be collected at screening, and EOS (as applicable). For continuous laboratory parameters, the observed values and changes from baseline will be summarized for each treatment group. For categorical laboratory parameters, frequency counts and percentages of subjects in each category will be provided.

Laboratory test results will be displayed in by-subject listings, and values outside of the normal reference range will be flagged.

Drug and alcohol screening and pregnancy results will be displayed in by-subject listings.

9.5 Vital Signs, Physical Measurements, and Physical Examinations

9.5.1. Vital Signs and Physical Measurements

Vital signs will be collected at screening, Day 1 prior to study gel administration (Day -1), Day 1, 2 (period 1), Day 8, 15 (period 2), and at the end of study visit on Day 8 or 22 (± 1 day).

Observed values and changes from baseline will be summarized using mean and change-from-baseline descriptive statistics for each treatment group, for the following measurements: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/minute), 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.

Body weight and height will be measured, and BMI will be calculated during the screening visit only. These values will be summarized along with other baseline characteristics for each treatment group. The number and percentage of subjects with potential clinically significant findings listed in Table 2 will be summarized for each treatment group. Vital signs will be displayed in a by-subject listing.

Table 2. List of Potential Clinically Significant Ranges for Vital Sign Parameters

Variable Name	*Low*	*High*
Systolic blood pressure	≤86 mm Hg OR a decrease of ≥25 mm Hg from baseline	≥200 mm Hg OR an increase of ≥25 mm Hg from baseline
Diastolic blood pressure	≤48 mm Hg OR a decrease of ≥20 mm Hg from baseline	≥110 mm Hg OR an increase of ≥20 mm Hg from baseline
Pulse	<45 bmp[1] OR a decrease of ≥25 bpm from baseline	>105 bpm and increase ≥25 bpm from baseline OR >125 bpm

9.6 Physical and Skin Examinations

Physical examinations are performed at screening, Day 1 prior to study gel administration (Day -1), Day 1, 2 (period 1), Day 8, 15 (period 2), and at the end of study visit on Day 8 or 22 (± 1 day).

Findings are recorded as normal or abnormal. Physical exam results will be displayed in a by-subject listing.

Skin examination will be performed according to the schedule in Table 2 of the protocol. Dermal responses collected from skin examination CRF will be displayed in a by-subject listing using following rating scales.

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.

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

9.7 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at screening, Day 1 prior to study gel application, as well as at the end of study visit on Day 8 or 22 (± 1 day).

The findings (i.e., classification as “normal,” “abnormal not clinically significant,” or “abnormal clinically significant”) will be recorded in the subject’s eCRF. ECG results will be summarized for each treatment group and displayed in a by-subject listing.

9.8 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

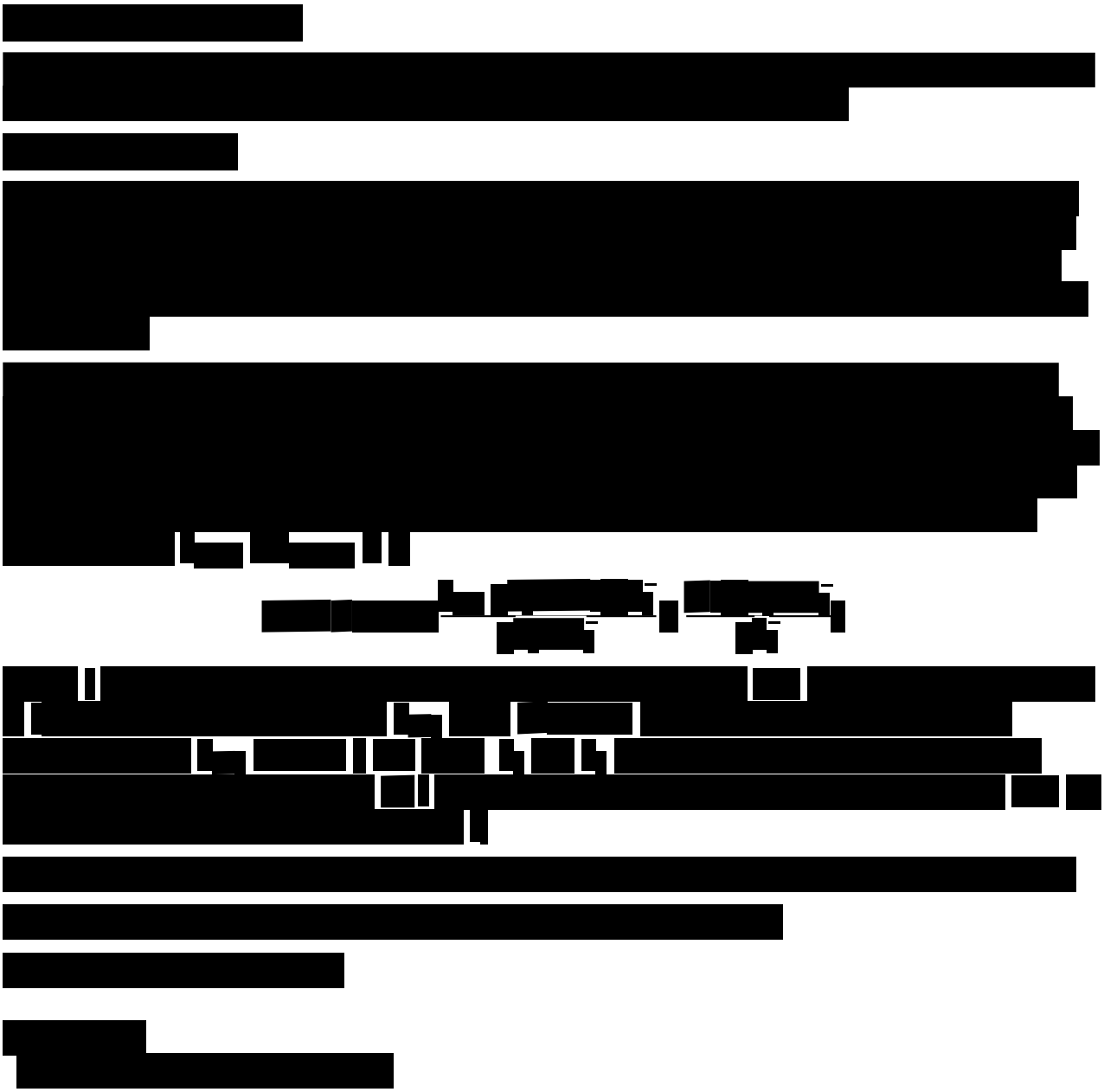
1 = Dried white residue was observed but no discomfort.

2 = Dried white residue was observed and slight discomfort (between 1 and 3)

3 = Dried white residue was observed and uncomfortable

10 PHARMACOKINETIC EVALUATION

Not applicable for this study.



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13 APPENDICES

13.1 Planned Tables, Figures and Listings for Analysis

13.1.1 Tables

Table Number	Table Title	Population
	Subject disposition and baseline characteristics	
Table 14.1.1.1	Summary of Subject Disposition (by Treatment Arm)	All Subjects Screened
Table 14.1.1.2	Summary of Subject Disposition (by Treatment Assignment)	All Subjects Screened
Table 14.1.2	Summary of Protocol Deviations (by Treatment Arm)	Randomized Subjects
Table 14.1.3.1.1	Summary of Demographics and Baseline Characteristics (by Treatment Arm)	Full Analysis Set
Table 14.1.3.1.2	Summary of Demographics and Baseline Characteristics (by Treatment Assignment)	Full Analysis Set
Table 14.1.3.2.1	Summary of Demographics and Baseline Characteristics (by Treatment Arm)	Per Protocol Set
Table 14.1.3.2.2	Summary of Demographics and Baseline Characteristics (by Treatment Assignment)	Per Protocol Set
Table 14.1.4	Summary of Medical History by System Organ Class and Preferred Term (by Treatment Arm)	Full Analysis Set
Table 14.1.5	Summary of Concomitant Medications, by ATC Class and Preferred Term (by Treatment Arm)	Full Analysis Set
	Efficacy Evaluations	
Table 14.2.1.1	Primary Endpoint: ANCOVA Results of Summed Pain Intensity Difference from T0 to T24 (SPID0-24) for the study leg while standing (by Treatment Arm)	Full Analysis Set
Table 14.2.1.2	Primary Endpoint: ANCOVA Results of Summed Pain Intensity Difference from T0 to T24 (SPID0-24) for the study leg while standing (by Treatment Arm)	Per Protocol Set
Table 14.2.2.1	ANCOVA Results of Sum of Pain Intensity Difference (SPID) 0-12, 0-24, 0-48, 0-72, [redacted]	Full Analysis Set
Table 14.2.2.2	ANCOVA Results of Sum of Pain Intensity Difference (SPID) 0-12, 0-24, 0-48, 0-72, [redacted]	Full Analysis Set

Table 14.2.2.3	Repeated Measures Analysis Results of Sum of Pain Intensity Difference (SPID) 0-12, 0-24, 0-48, 0-72, [redacted] for K-285 Group	Full Analysis Set
Table 14.2.2.4	Repeated Measures Analysis Results of Sum of Pain Intensity Difference (SPID) 0-12, 0-24, 0-48, 0-72, [redacted] for K-285 Group	Full Analysis Set
Table 14.2.2.5	Repeated Measures Analysis Results of Sum of Pain Intensity Difference (SPID) 0-12, 0-24, 0-48, 0-72, [redacted] for Menthol Group	Full Analysis Set
Table 14.2.2.6	Repeated Measures Analysis Results of Sum of Pain Intensity Difference (SPID) 0-12, 0-24, 0-48, 0-72, [redacted] for Menthol Group	Full Analysis Set
Table 14.2.2.8	Primary Endpoint: ANCOVA Results of Summed Pain Intensity Difference from T0 to T24 (SPID0-24) for the Study Leg while Standing (by Treatment Arm) – Each Multiple Imputed Dataset	Full Analysis Set
Table 14.2.3.1	[redacted]	Full Analysis Set
Table 14.2.3.2	[redacted]	Full Analysis Set
Table 14.2.4.1	[redacted]	Full Analysis Set
Table 14.2.4.2	[redacted]	Full Analysis Set
Table 14.2.5.1	[redacted]	Full Analysis Set
Table 14.2.5.2	[redacted]	Full Analysis Set
Table 14.2.8.1	[redacted]	Full Analysis Set

Table 14.2.9.1	Proportion of subjects with onset of perceptible pain relief between 0 to 6 hours, 0 to 24 hours for study leg while standing and at rest (by Treatment Arm)	Full Analysis Set
Table 14.2.9.2	Proportion of subjects with onset of meaningful pain relief between 0 to 6 hours, 0 to 24 hours for study leg while standing and at rest (by Treatment Arm)	Full Analysis Set
Table 14.2.10	Summary of Rescue Medication (by Treatment Arm)	Full Analysis Set
Safety Evaluations		
Table 14.3.1.1.1	Overall Summary of Treatment-Emergent Adverse Events (by Treatment Arm)	Safety Population
Table 14.3.1.1.2	Overall Summary of Treatment-Emergent Adverse Events (by Treatment Assignment)	Safety Population
Table 14.3.1.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (by Treatment Arm)	Safety Population
Table 14.3.1.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term (by Treatment Assignment)	Safety Population
Table 14.3.1.4.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (by Treatment Arm)	Safety Population
Table 14.3.1.4.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (by Treatment Assignment)	Safety Population
Table 14.3.1.5.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug (by Treatment Arm)	Safety Population
Table 14.3.1.5.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug (by Treatment Assignment)	Safety Population
Table 14.5.1.1	Summary of Chemistry Results and Change from Baseline by Time Point (by Treatment Arm)	Safety Population
Table 14.5.1.2	Summary of Hematology Results and Change from Baseline by Time Point (by Treatment Arm)	Safety Population
Table 14.5.1.3	Summary of Continuous Urinalysis Results and Change from Baseline by Time Point (by Treatment Arm)	Safety Population
Table 14.5.1.4	Summary of Categorical Urinalysis Results by Time Point (by Treatment Arm)	Safety Population

Table 14.6.1	Summary of Vital Signs: Results and Change from Baseline by Time Point (by Treatment Arm)	Safety Population
Table 14.6.2	Summary of Potential Clinically Significant Vital Sign Parameters (by Treatment Arm)	Safety Population
Table 14.7.1	Summary of Physical Examination Results (by Treatment Arm)	Safety Population
Table 14.8.1	Summary of ECG Results (by Treatment Arm)	Safety Population
Table 14.9.1	Summary of Skin Examination (Dermal Responses and Other Effects) (by Treatment Arm)	Safety Population
Table 14.9.2	Summary of Skin Examination (Dermal Responses and Other Effects) (by Treatment Assignment)	Safety Population
Table 14.10.1	Summary of Study Drug Compliance (by Treatment Arm)	Safety Population
Table 14.11.1	Subject's Impression of Dried White Gel Residue (by Treatment Arm)	Safety Population

13.1.2 Listings

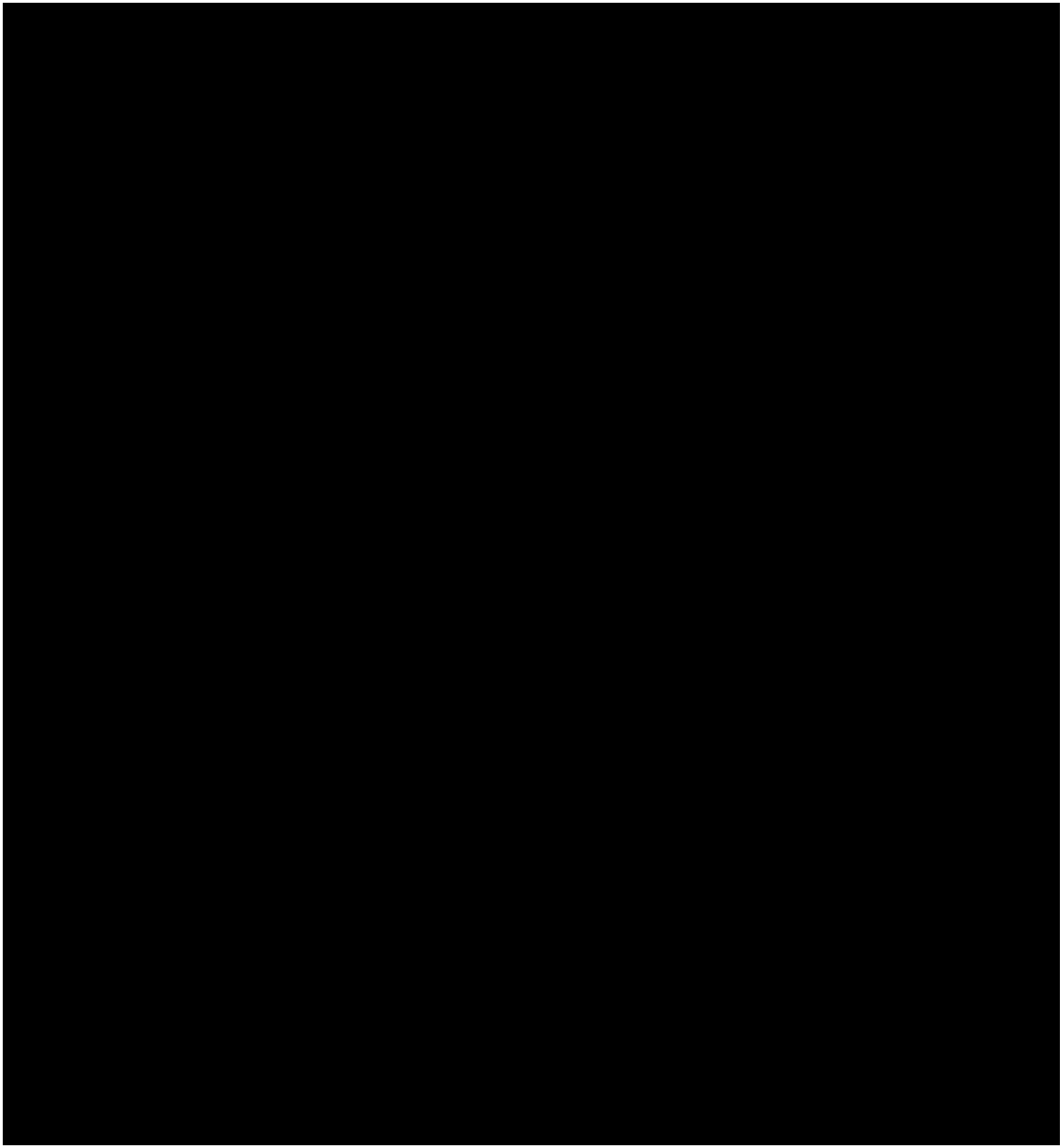
Listing Number	Listing Title	Population
Listing 16.2.1.1	Randomization and Study Population	All Patients Screened
Listing 16.2.1.2	Informed Consent and Re-Consent	All Patients Randomized
Listing 16.2.1.3	Screen Failure	All Patients Screened
Listing 16.2.1.4	Subject Populations and Reasons Excluded from Analysis Sets	All Patients Screened
Listing 16.2.1.5	Subject Completion / Early Termination	All Patients Randomized
Listing 16.2.2	Protocol Deviations	All Patients Randomized
Listing 16.2.3.1	Demographics and Baseline Characteristics	Full Analysis Set
Listing 16.2.3.2	Medical / Surgical History	Full Analysis Set
Listing 16.2.3.3	Concomitant Medications	Full Analysis Set
Listing 16.2.3.4	Rescue Medication Administration	Full Analysis Set
Listing 16.2.3.5	eVAS Record	Full Analysis Set
Listing 16.2.3.6.1	Sum of Pain Intensity Difference (SPID) in eVAS scores	Full Analysis Set
Listing 16.2.3.6.2	eVAS Scores and Sum of Pain Intensity Difference (SPID) for Study Leg While Standing (0-24 Hours) - Imputed	Full Analysis Set
Listing 16.2.3.7	Time to Pain Relief	Full Analysis Set
Listing 16.2.4.1	Study Drug Administration, Pain Assessment Training, and Discharge	Safety Population
Listing 16.2.4.2	Study Drug Compliance	Safety Population
Listing 16.2.5.1	Adverse Events	Safety Population

Listing 16.2.5.2	Serious Adverse Events	Safety Population
Listing 16.2.5.3	Treatment Related Adverse Events	Safety Population
Listing 16.2.5.4	Adverse Events Leading to Study Discontinuation	Safety Population
Listing 16.2.5.5	Adverse Events Leading to Death	Safety Population
Listing 16.2.6.1	Chemistry Laboratory Test Results	Safety Population
Listing 16.2.6.2	Coagulation Laboratory Test Results	Safety Population
Listing 16.2.6.3	Hematology Laboratory Test Results	Safety Population
Listing 16.2.6.4	Urinalysis Laboratory Test Results	Safety Population
Listing 16.2.6.5	Alcohol and Urine Drug Screen Tests	Safety Population
Listing 16.2.6.6	Pregnancy Test	Safety Population
Listing 16.2.7.1	12-Lead Electrocardiogram	Safety Population
Listing 16.2.7.2	Vital Signs	Safety Population
Listing 16.2.7.3	Dermal Responses and Other Effects	Safety Population
Listing 16.2.7.4	Residue Evaluation	Safety Population

13.1.3 Figures

Figures Number	Figure Title	Population
Figure 14.2.1	Mean (SE) of VAS Change from Baseline for the Study Leg while Standing (by Treatment Arm)	Full Analysis Set
Figure 14.2.2	Mean (SE) of VAS Change from Baseline for the Study Leg at Rest (by Treatment Arm)	Full Analysis Set
Figure 14.2.3	Mean (SE) of VAS Change from Baseline While Standing by Study and Non-Study Leg for K-285 Group	Full Analysis Set
Figure 14.2.4	Mean (SE) of VAS Change from Baseline While Standing by Study and Non-Study Leg for Menthol Group	Full Analysis Set
Figure 14.2.5	Mean (SE) of VAS Change from Baseline at Rest by Study and Non-Study Leg for K-285 Group	Full Analysis Set
Figure 14.2.6	Mean (SE) of VAS Change from Baseline at Rest by Study and Non-Study Leg for Menthol Group	Full Analysis Set
Figure 14.3.1	Mean (SE) of VAS for the Study Leg while Standing (by Treatment Arm)	Full Analysis Set
Figure 14.3.2	Mean (SE) of VAS for the Study Leg at Rest (by Treatment Arm)	Full Analysis Set
Figure 14.3.3	Mean (SE) of VAS While Standing by Study and Non-Study Leg for K-285 Group	Full Analysis Set
Figure 14.3.4	Mean (SE) of VAS While Standing by Study and Non-Study Leg for Menthol Group	Full Analysis Set

Figure 14.3.5	[redacted]	Full Analysis Set
Figure 14.3.6	[redacted]	Full Analysis Set
Figure 14.4.1	Kaplan-Meier Plot for Time to first dose of Rescue Medication (by Treatment Arm)	Full Analysis Set
Figure 14.5.1	Kaplan-Meier Plot for Time to first onset of Perceptible Pain Relief for Study Leg while standing and at rest (by Treatment Arm)	Full Analysis Set
Figure 14.5.2	[redacted]	Full Analysis Set
Figure 14.5.3	Kaplan-Meier Plot for Time to first onset of Meaningful Pain Relief for Study Leg while standing and at rest (by Treatment Arm)	Full Analysis Set
Figure 14.5.4	[redacted]	Full Analysis Set



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