Statistical Analysis Plan

Protocol Title:	Randomized, Double-Blind, Multi-Center, Parallel-Group Comparison of the Efficacy and Safety of the C213 (Zolmitriptan Intracutaneous Microneedle System) to Placebo for the Acute Treatment of Cluster Headaches
Protocol Number:	Protocol No. CP-2019-001 (27 June 2019), Amendment 1, Dated 16 July 2019, Amendment 2, Dated 01 October 2019 and Amendment 3, Dated 15 April 2020
Investigational Product:	C213 (Zolmitriptan Intracutaneous Microneedle System)
Dose	Single-dose treatment (to be applied for 30 minutes to the upper arm) of 1.9 mg or 3.8 mg
Phase:	2/3
Sponsor:	Zosano Pharma Corporation 34790 Ardentech Court Fremont, CA 94555
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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ADaM	Analysis Data Model
BMI	Body Mass Index
CI	Confidence Interval
CMH	Cochran Mantel Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
EDC	Electronic Data Capture
eDiary	Electronic Diary
e.g.	*Exempli gratia* (for example)
EMA	European Medicines Agency
ET	Early Termination
FDA	Food and Drug Administration
ICH	International Council for Harmonization
i.e.	*id est* (that is)
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
N, n	Number (of subjects)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol CP-2019-001: A randomized, double-blind, multi-center, parallel-group comparison of the efficacy and safety of the C213 (Zolmitriptan Microneedle System) to placebo for the acute treatment of cluster headaches, dated 27 June 2019, Amendment 1, dated 16 July 2019, Amendment 2, dated 01 October 2019 and Amendment 3, dated 15 April 2020.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by FDA, European Medicines Agency (EMA), and International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned exploratory analysis performed will be clearly identified as such in the final CSR.

In preparation of this SAP, the following documents were reviewed and considered in addition to the literature references cited in this SAP:

- Clinical Research Protocol CP-2019-001 Final v1.0 issued 27 June 2019, Amendment 1, dated 16 July 2019, Amendment 2, dated 01 October 2019 and Amendment 3, dated 15 April 2020.
- Case report forms (CRFs) for Protocol CP-2019-001
- ICH Guidance on Statistical Principles for Clinical Trials (E9)
- FDA response to meeting request dated 07 February 2019

Per FDA request, Amendment 3 incorporated changing time zero from the time of the second patch application to be the time of the first patch application, so that the primary efficacy endpoint would be measured at 15 minutes from the start of dosing.

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare the efficacy of C213 at doses of 1.9 mg and 3.8 mg (1.9 mg x 2 patches) to placebo in the acute treatment of cluster headache attacks.

2.1.2 Secondary Objectives

The secondary objective is to compare the safety of C213 at doses of 1.9 mg and 3.8 mg (1.9 mg x 2 patches) to placebo and to assess the dose-response relationship of C213 on

efficacy and tolerability.

2.2 Study Endpoints

2.2.1 Efficacy Endpoints

The co-primary efficacy endpoints are:

- The proportion of subjects who achieve pain relief at 15 minutes and the proportion of subjects who achieve sustained pain relief from 15 minutes to 60 minutes. Headache pain is assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Pain relief is defined by a decrease in pain from severe to mild or none without the use of acute rescue medication. Sustained pain relief requires a pain rating of mild or none at each timepoint from 15 minutes to 60 minutes without the use of acute rescue medication. The co-primary efficacy endpoints will compare the 1.9 mg and 3.8 mg treatment arms separately to placebo.

Secondary efficacy endpoints:

- Proportion of subjects that achieve pain relief at 5, 10, 20 and 30 minutes post patch application
- Proportion of subjects that achieve sustained pain relief from 5 to 60 minutes and from 10 to 60 minutes post patch application
- Proportion of subjects that achieve pain freedom at 10 and at 15 minutes post patch application
- Proportion of subjects that achieve sustained pain freedom from 10 to 60 minutes and from 15 to 60 minutes post patch application
- Proportion of subjects using rescue therapy within 20 minutes post patch application
- Proportion of subjects able to perform their usual daily activities as assessed by the subject at 5, 10, 15, 20, 30 and 60 minutes post patch application

2.2.2 Safety Endpoints

Safety will be assessed by:

- Incidence of adverse events (AEs)
- Physical examination findings
- Vital signs including blood pressure
- Clinical laboratory determinations including coagulation studies
- Serum pregnancy and urine pregnancy for women of child-bearing potential
- 12-lead electrocardiogram (ECG) parameters

- Assessment of concomitant medications
- Investigator visual skin assessments

3. OVERALL STUDY DESIGN AND PLAN

This is a phase 2/3, randomized, multicenter, double-blinded, placebo-controlled study that will investigate the efficacy and safety of C213 in the acute treatment of cluster headache attacks. Subjects who have consented and meet the entry criteria will be randomized to receive one of three blinded treatments. Approximately 120 subjects will be randomized. The study is to be conducted at approximately 13 investigational sites in the United States.

Qualified subjects will be randomized to the double-blind treatment period on Day 1 and will have up to 48 weeks to confirm and treat one cluster headache. Using an electronic diary (eDiary) to confirm the subject is experiencing a cluster headache, subjects will self-administer the patches and respond to questions in the eDiary until 1-hour post treatment.

The total duration of this study could be up to approximately 50 weeks over 3 visits, with up to 48 weeks of treatment duration and a variable length of screening (up to 10 days). This study will consist of a Screening visit (Visit 1, up to 1 week prior to randomization), Randomization visit (Visit 2, Day 1), up to a 48-week treatment period (Day 1 - Day 336), and End of Study/Early Discontinuation visit (Visit 3, 1-8 days post-treatment).

Screening activities may be completed over a period as short as one day or spread out over up to one week. At Visit 2, subjects will return to the site for additional baseline assessments and randomization (Day 1). If they meet all study randomization criteria, they will be randomly assigned in a 1:1:1 ratio to receive C213 1.9 mg administered as one active and one placebo patch, C213 3.8 mg administered as two active patches, or placebo administered as two placebo patches.

3.1 Selection of Study Population

For a complete list of inclusion and exclusion criteria please refer to the initial protocol issued 27 June 2019, Amendment 1, dated 16 July 2019, Amendment 2, dated 01 October 2019 and Amendment 3, dated 15 April 2020.

3.2 Method of Treatment Assignment and Randomization

To be eligible for randomization and the double-blind period, subjects must meet all inclusion and no exclusion criteria. In addition, the following must be confirmed on the day of randomization:

1. Demonstrated ability to properly use the eDiary

2. Willing to enter eDiary data to determine if he/she is experiencing a qualifying cluster headache attack and complete the eDiary questions after applying the patches
3. Demonstrated ability to apply the demonstration study drug patches
4. Confirmation of continuing good general health, or stable non-serious disease that in the opinion of the Investigator will not place the subject at risk

3.3 Treatment Blinding

This is a double-blind study. Unless otherwise specified, all study personnel are to remain blinded to study drug. Treatment assignments will not be revealed until all subjects have completed the study and the database has been finalized and closed.

If a medical emergency occurs and a decision regarding the subject's clinical treatment requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Unless the medical emergency is deemed to be life-threatening, the medical monitor must first be consulted before unblinding.

3.4 Minimization of Missing Data / Dropout rate

It is important to avoid missing data from clinical trials. The following strategies are designed to minimize drop-outs and missing data in this study:

- Minimizing the burden on subjects, with only three visits scheduled over the course of the trial (with reasonable visit window flexibility).
- Providing payment for subjects' time at clinic visits, as approved by the Institutional Review Board.
- Allowing rescue medication/therapy at or after 20 minutes post patch administration.
- Training of site personnel on emphasizing to subjects the importance of completing the eDiary assessments in order to minimize missing data.
- Employing an eDiary training module for subjects to complete prior to the distribution of the eDiary.
- Using alarms and reminder alerts for eDiary data entry.
- Instituting an eDiary reminder card for subject use that shows the timepoints when subjects need to enter data.
- Having a web portal available to site personnel where missing eDiary data can be easily identified so site personnel can be retrained on the importance of emphasizing to subjects the need to complete eDiary assessments, if necessary.

Due to the COVID-19 pandemic, the protocol was amended in April 2020 to allow for a visit 3 telemedicine visit. If any subjects cannot or elect not to be seen in clinic, the Visit

3/End of Study Visit may take place via a virtual video (such as FaceTime, WhatsApp, Skype, Zoom). During this call, the Principal Investigator will assess for adverse events, skin reactions where C213 was applied, concomitant medication/rescue medication use, and drug accountability. For the subjects who are female of child-bearing potential, the sites will send a urine pregnancy test kit (monthly per protocol) and after dosing, verify that there is no pregnancy. In addition, the Sponsor, on a case by case basis, will consider allowing an 'out of window' Visit 3/End of Study Visit (in person). Any procedure such as vital signs, blood collection, and ECG which cannot be collected on site or remote will be indicated as 'not done' in both the source documents and eCRF, and if prompted, with a reason specified in the eCRF as due to the pandemic.

4. ANALYSIS AND REPORTING

4.1 Interim Analysis

There is no interim analysis planned for this study.

4.2 Final Analysis

All final, planned analyses will be performed after the last subject has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

5. SAMPLE SIZE DETERMINATION

The study is planned to enroll approximately 120 subjects total in a 1:1:1 randomization, that is, 40 subjects in each of the placebo, C213 1.9 mg, and C213 3.8 mg groups. It is anticipated that 20% of subjects receiving placebo and 55% of subjects receiving active treatment will achieve pain relief at 15 minutes and sustained pain relief from 15 minutes to 60 minutes post-dose. Based on a two-sided chi-square test with continuity correction and an alpha level of 0.05, 40 subjects per arm will provide approximately 80% power to detect this same difference between two treatment groups, assuming a 15% dropout rate.

6. ANALYSIS POPULATIONS

The following analysis populations are planned for this study:

- **Safety Population:** The safety population will include all subjects who received any amount of study drug. All safety analyses will be performed using this population, analyzed as treated.
- **Modified Intention-To-Treat Population (mITT)**: All randomized subjects who have a qualifying headache and at least one post-application pain score recorded within the first 15 minutes post-application will be included in the mITT population. This is the primary population for efficacy analyses and subjects will be analyzed based on their randomized treatment.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment group.

Baseline characteristic and safety tables will be completed for the Safety Population unless otherwise specified. Efficacy tables will be presented for the mITT Population.

Continuous, quantitative, variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical, qualitative, variable summaries will include the frequency and percentage of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group unless otherwise specified.

Baseline values are defined as the last non-missing measurement prior to patch administration. Change from baseline will be defined as the post-baseline visit value minus the baseline value.

Subjects are not supposed to change study sites; however, should this be necessary to allow a subject to continue in the study, subjects will be analyzed under the site where they were initially enrolled.

Study day after patch administration is defined as assessment date – patch administration date +1. Dates prior to patch administration are defined as assessment date – patch administration date.

All analyses will be performed using Statistical Analysis System (SAS®) Software version 9.3 or later.

7.1.1 Adjustments for Multiplicity and Other Alpha Control

There will be no adjustments made for multiplicity to control the overall type I error.

7.1.2 Data Handling for Subjects Who Withdraw from the Study

Subjects who withdraw/drop out from the study will have their early termination (ET) visit data collected within 1-8 days following the time of the subject's early termination. Safety data will be included in the Visit 3 end of study summaries as appropriate per the definition of the safety population. The subjects' efficacy data will be included in the efficacy analyses according to the definition of mITT.

7.1.3 Methods for Handling Missing Data

Missing pain and daily activities data for participants in the mITT population will be imputed via last observation carried forward (LOCF). Prior to imputing missing endpoint data for the endpoint sustained pain relief 15-60 minutes, pain relief will be assessed at each of the 15, 20, 30, and 60-minute timepoints that have data available. If any of these

timepoints has a pain severity rating of moderate or severe, or if the subject has used a rescue medication/therapy, then the subject will be considered to have not achieved sustained pain relief and this endpoint will not be imputed. Otherwise, missing pain data will be imputed using LOCF. Missing data for all sustained pain relief and sustained pain freedom endpoints will be handled this way.

Missing safety data will not be imputed. Due to COVID-19, it is unavoidable that some subjects will be missing certain safety assessments, such as (but not limited to) Visit 3 clinical labs, vital signs, and ECG. This is because the Visit 3 occurred during the pandemic and telemedicine visit was necessary. Safety summaries will be generated using observed data, and missing safety assessments will be captured as protocol deviations.

Missing rescue medication data will be handled as described in section 7.2.4.4.

7.2 Efficacy Assessments

There are two primary efficacy endpoints. Other secondary and exploratory efficacy endpoints are tested to better understand the potential clinical benefit of C213 on cluster headache subjects.

7.2.1 Co-primary Efficacy Endpoints

7.2.2 Pain Relief

One of the co-primary efficacy endpoints is the proportion of subjects who achieve pain relief at 15 minutes post patch administration. Headache pain will be assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), with pain relief defined by a decrease in pain from severe to mild or none, without the use of acute rescue medication within 15 minutes post patch administration. Subjects record their answers in the eDiary to the question: “How bad is your headache pain?”. Subjects are also asked in the eDiary, “Did you take any medication, since your last diary entry, other than the patches you applied to treat your headache?” in order to assess rescue medication use (see section 7.2.4.4).

7.2.3 Sustained Pain Relief

The other co-primary efficacy endpoint is the proportion of subjects who achieve sustained pain relief from 15 minutes to 60 minutes post patch administration. Sustained pain relief requires a pain rating of mild or none at each timepoint from 15 minutes to 60 minutes without the use of acute rescue medication at any time during the 60 minutes post patch administration.

7.2.4 Secondary Efficacy Assessments

7.2.4.1 Pain Freedom

Pain freedom is defined by a rating of none using the 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) without the use of acute rescue medication up until the timepoint being assessed (10 or 15 minutes).

7.2.4.2 Sustained Pain Freedom

Sustained pain freedom requires a pain rating of none at each timepoint from 10 (or 15) minutes to 60 minutes without the use of acute rescue medication at any time during the 60 minutes post patch administration.

7.2.4.3 Pain Relief and Sustained Pain Relief

Secondary endpoints of pain relief (at 5, 10, 20, and 30 minutes post patch administration) and sustained pain relief (5 and 10 minutes to 60 minutes post patch administration) will be assessed in the same manner as the primary endpoints. For example, pain relief at 5 minutes requires a rating of mild or none without the use of acute rescue medication within 5 minutes post patch administration. Sustained pain relief requires a pain rating of none at each timepoint from 5 (or 10) minutes to 60 minutes without the use of acute rescue medication at any time during the 60 minutes post patch administration.

7.2.4.4 Rescue Medication/Therapy Use

A subject is considered to have taken a rescue medication by a given timepoint if the answer to the eDiary question, 'Did you take any medication, since your last diary entry, other than the patches you applied to treat your headache?' is answered Yes at that timepoint or any preceding timepoint. The specific medication/therapy is to be recorded as a concomitant medication in the CRF.

If rescue medication use data are missing for a given timepoint and there are no "Yes" responses at a previous timepoint, missing values will be imputed using the next available value (next observation carried backward). If rescue medication data are still missing after imputation, then it will be assumed a rescue medication was not taken. For the 60-minute timepoint, if rescue medication use data are missing at 60 minutes and there are no "Yes" responses at a previous timepoint, then the subject is considered not to have taken the rescue medication by the 60-minute timepoint.

7.2.4.5 Ability to Perform Daily Activities

Whether or not subjects are able to perform their usual daily activities is assessed by subject responses (Yes or No) in the eDiary to the question, "Do you feel able to perform your usual daily activities?" If a subject responds "Yes" but has used a rescue medication, the subject is considered as not being able to perform the usual daily activities.

7.3 Safety Assessments

Safety will be assessed by:

- AEs and serious adverse events (SAEs)
- Clinical laboratory test results including coagulation
- Vital signs (heart rate, blood pressure, respiration rate, temperature)
- Abnormal physical examination findings
- Abnormal 12-lead ECG parameters (HR, RR, PR, QRS, QT, QTcB, QTcF)
- Ratings from Investigator visual skin assessments

7.3.1 Adverse Event and Prior/Concomitant Medication handling conventions

To handle missing or partial AE and prior/concomitant medication dates, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the first dose date, then impute the month and day of the first dose date.
    b. Otherwise, assign “January.”
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the first dose date.
    b. Otherwise, assign “01.”

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign “December.”
3. If the day is unknown, then assign the last day of the month.

Adverse events are categorized as either pre-treatment adverse events or treatment-emergent adverse events based on the response to the CRF question “Did the AE occur prior to patch administration?”

After implementing the rules above, to determine whether medications with missing start or stop dates are prior or concomitant medications, the following strategy will be used:

1. If the start date and stop date are both missing, then the medication is considered to be both a prior and a concomitant medication.
2. If the start date is missing but the stop date is not missing and is before the day of patch administration, then the medication is considered to be a prior medication, otherwise it is considered to be both prior and concomitant.
3. If the stop date is missing but the start date is not missing and is on or within 5 days after the date of patch application, then the medication is considered to be concomitant.
4. If the stop date is missing but the start date is not missing and is prior to the date of patch application, then the medication is considered to be both prior and concomitant.

The missing severity of an AE will be imputed to "severe"; the missing relationship to study drug of an AE will be imputed to "related".

8. STUDY SUBJECTS AND DEMOGRAPHICS

8.1 Disposition of Subjects and Withdrawals

The numbers and percentage of subjects randomized, completing the study, and withdrawing from the study, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number and percentage of subjects in each analysis population will be reported.

8.2 Protocol Deviations

Protocol deviations will be checked on complete data for all subjects, determined during a (blinded) data review meeting before database lock, unblinding, and the final analysis. Protocol deviations are collected on the CRF.

Protocol deviations will be summarized by treatment group for the Safety population. Protocol "violations" are not differentiated from deviations; instead, each deviation is identified either as "major" or "minor" depending upon its potential impact upon the integrity of the study data or the subject's well-being. Any deviation related to the COVID-19 pandemic is required to be entered in the EDC by the investigational site with the word ***COVID*** entered as prefix to the deviation texts.

Individual subjects with protocol deviations will be listed.

8.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for all subjects in the safety population by treatment groups.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age, gender, race/ethnicity, height, weight, body mass index (BMI), alcohol use, smoking history, and illicit drug use). In addition to the safety population, these will also be repeated for all randomized subjects and the mITT population.

- Cluster headache history characteristics such as type (chronic or episodic) and each subject's usual signs and symptoms. The number of years since first cluster headache will be calculated using the following formula: ([year of informed consent]-[year of first cluster attack]).

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and summarized by System Organ Class (SOC) and Preferred Term using frequency counts by treatment group.

9. EFFICACY ANALYSES

9.1 Primary Efficacy Analysis

The proportion of subjects who achieve pain relief at 15 minutes and the proportion who achieve sustained pain relief from 15 minutes to 60 minutes post patch administration will be analyzed separately using Fisher's Exact test, with missing data imputed using LOCF (see section 7.1.3). The analyses will include all subjects in the mITT population. A significance test of the treatment difference comparing each C213 dose (1.9 mg and 2.8 mg) to placebo will be tested at the two-sided 0.05 level.

9.1.1 Sensitivity and Supporting Analyses

The primary analysis may be followed by a sensitivity analysis to investigate the impact of missing data on the treatment estimates.

9.1.1.1 C213 patients as failure and placebo as responder

If performed, this sensitivity analysis will be a repeat of the primary efficacy analysis where C213 patients with missing data will be imputed as non-responders/failures, and placebo patients with missing data as responders. Thus, for the co-primary outcome measure of pain relief at 15 minutes, C213 patients with a missing pain score at 15 minutes will be considered a treatment failure, and placebo patients with missing data at 15 minutes will be considered a responder. For the co-primary outcome measure of sustained pain relief, C213 patients with a missing pain score at any time from 15-60 minutes will be considered a treatment failure, and placebo patients with a missing pain score will be considered a responder only if all other pain scores within 15-60 minutes are not severe or are missing.

9.2 Secondary Efficacy Analyses

Binary data, with the exception of rescue therapy use, will be summarized by treatment group. Missing data will be imputed using LOCF. Summaries of the proportion of subjects will be calculated and displayed, and a Fisher's Exact test will be performed. Two-sided p-values for the test of no difference between each C213 treatment group and placebo will be provided. Rescue therapy use as reported on the eDiary will be listed by subject and timepoint.

These endpoints will include:

- Proportion of subjects that achieve pain relief at 5, 10, 20, and 30 minutes post patch application
- Proportion of subjects that achieve sustained pain relief from 5 to 60 minutes and from 10 to 60 minutes post patch application
- Proportion of subjects that achieve pain freedom at 10 minutes and 15 minutes post patch application
- Proportion of subjects that achieve sustained pain freedom from 10 to 60 minutes and from 15 to 60 minutes post patch application
- Proportion of subjects using rescue therapy within 20 minutes post patch application
- Proportion of subjects able to perform their usual daily activities as assessed by the subject at 5, 10, 15, 20, 30, and 60 minutes post patch application

9.3 Exploratory Efficacy Analyses

Depending on sample size, the primary efficacy analyses were to be conducted for the subgroup of patients in the mITT population who were in the trial prior to Protocol Amendment 3 and for those who were enrolled after Amendment 3, with the purpose of assessing the impact of the modification of time zero to be the start of the first patch application.

10. SAFETY AND TOLERABILITY ANALYSIS

The safety analysis will be run on the Safety population. The analysis of safety assessments in this study will include summaries or data listings of the following safety and tolerability data collected for each subject:

- Adverse Events including Serious Adverse Events
- Clinical Laboratory Investigations including coagulation studies
- Concomitant Medications
- Vital Signs
- Physical exam including height and weight
- Investigator visual skin assessments
- Electrocardiogram Parameters
- Pregnancy Tests

10.1 Adverse Events

All AEs, treatment-emergent adverse events (TEAEs), and SAEs will be coded using MedDRA, version 22.0.

Adverse events are categorized as either pre-treatment adverse events or treatment-emergent adverse events based on the response to the CRF question "Did the AE occur prior to patch administration?"

An AE summary table or listing will be presented for the following:

- TEAEs by severity
- TEAEs leading to study drug discontinuation
- TEAEs by relationship
- SAEs

Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA SOC and preferred term will be prepared if there are a sufficient number of adverse events.

Each subject will be counted only once within each summation level (SOC; preferred term).

In the AE data listings, all AEs will be displayed. AEs that are treatment-emergent will be flagged.

10.1.1 Adverse Events Leading to Discontinuation of Study Drug

A listing of AEs leading to discontinuation of study drug will be provided, displaying details of the event(s) captured on the CRF.

10.1.2 Serious Adverse Events

A listing of SAEs will be provided, displaying details of the event(s) captured on the CRF.

10.1.3 Deaths

A listing of deaths will be provided for the Safety Population.

10.2 Clinical Laboratory Evaluations

Laboratory tests will be performed at the Screening and End of Study (or early discontinuation) visits and include analytes for Serum Chemistry and Hematology. Pregnancy tests will be performed on all women of child-bearing potential at screening and every month [+ or – 7 days] after randomization to ensure no pregnancy prior to study drug administration. The urine drug abuse screen will be performed at screening and will test for amphetamines, barbiturates, cocaine, phencyclidine (PCP), and meth/amphetamines.

Laboratory values will be displayed in the by-subject data listings for the Safety Population and those that are outside the normal range ("H" or "L") will be flagged,

along with corresponding normal ranges. Pregnancy data collected throughout the study will be listed, as well as results from the urine drug abuse screen.

10.3 Vital Signs

All subjects will have vital signs (temperature, RR, BP, and HR) measured at the Screening, Randomization (Day 1), and End of Study (or early discontinuation) visits.

A by-subject listing of all vital sign data will be provided.

10.4 Physical Examination

A physical examination including height and weight will be performed during the Screening, Randomization (Day 1), and End of Study (or early discontinuation) visits. Height will be collected at screening only. The physical examination will include, but is not limited to, HEENT, dermatologic (investigator skin assessment), brief neurological, general appearance, lymph nodes, cardiovascular, respiratory, gastrointestinal, and musculoskeletal examination.

Abnormal PE findings will be listed by subject; clinical significance will be indicated as well as the abnormality specified. In addition, a by-subject listing height and weight data will be generated.

10.5 Electrocardiogram (ECG)

A 12-lead ECG will be performed at the Screening and End of Study (or early discontinuation) visits. The standard ECG parameters including rhythm, heart rate, and intervals for PR, QRS, QT, QTcB and QTcF (Fridericia's) correction for heart rate will be recorded. A listing of abnormal ECGs will be generated along with clinical significance as determined by the Investigator, any Investigator comments, and the results for all ECG parameters. A by-subject data listing of all ECG results will also be provided for each visit.

10.6 Investigator Visual Skin Assessment

The Investigator will perform a visual skin assessment of bruising, erythema, and edema at the randomization visit (Visit 2) and at the End of Study (or early discontinuation) visit. Any adverse events including application site reactions will be documented on the appropriate eCRF page and must be followed until resolution or medically stable.

At the End of Study (or early discontinuation) visit, the entire surface area of the outer upper arm where the two patches were applied will be assessed for the following skin signs or symptoms. Any findings with an intensity rating of 1 (Mild intensity), 2 (Moderate intensity), or 3 (Severe intensity) must be recorded as an adverse event in the eCRF and followed to resolution.

Bruising assessments (visual rating) will be performed using the following ratings:

Symptom	Intensity Rating (circle)
Bruising where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

The following ratings will be used to describe the amount of erythema and edema indicative of irritation:

Symptom	Rating (circle)
Skin Erythema where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

Symptom	Rating (circle)
Skin Edema where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

A by-subject data listing for bruising, erythema, and edema will be provided for each subject that has a rating of anything but ‘Clear’ at any visit and for those subjects who did not have the investigator skin assessment performed.

11. MEDICATIONS

11.1 Concomitant Medications

All medications will be coded using WHODrug-Global-B3 version March 2019. Prior and concomitant medications will be summarized by treatment group and by the number and percentage of subjects taking each medication, classified by using WHO-DD Anatomical Therapeutic Chemical Level 3 and preferred term.

Prior medications are defined as medications or therapies initiated prior to the start of patch administration. Concomitant medications are defined as any medications other than the study drug that a subject receives concurrently with the study drug. These medications will have start dates on, prior to, or within 5 days after the date of patch administration and end dates on or after the date of patch administration. Any medication that was stopped more than 90 days prior to informed consent will not be considered prior or concomitant.

Prior and Concomitant medications will be summarized. All medications will be presented in a listing.

Please refer to Section 7.3 for the conventions used to impute partial start dates and end dates of concomitant medications.

11.2 Extent of Exposure

Treatment duration is defined as 30 minutes (time that the patch should remain on the subject).

Extent of exposure to study medication will be tabulated by treatment group by summarizing the frequency and percentage of subjects whose patch stayed on for 30 minutes as collected in the CRF.

A listing of drug accountability data based on CRF data will be provided.

12. CHANGES FROM PLANNED ANALYSIS

Due to insufficient enrollment numbers, the CMH test as described in the protocol for the primary and secondary analyses will not be performed. The protocol also describes a fixed sequential procedure to control for overall type 1 error. This will not be implemented since the actual number of randomized subjects is quite a bit less than planned and the pre-specified statistical analyses as described in the protocol cannot be performed.

13. APPENDICES

13.1 Appendix 1

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

13.1.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a clinical study report (CSR).
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, listings, and graphs (TLGs).
- All footnotes will be left justified at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the TLG. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in mixed HHhr MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show

the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

- All TLGs will have the name of the program, location, and a date stamp on the bottom of each output.
- All analysis programs developed for a TLG display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

13.1.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "<name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) All Subjects, (b) ITT, (c) Safety, and (d) PP.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of Subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: n, mean, SD, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 95% confidence intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x%). A percentage of 100% will be reported as 100%. A percentage of zero will be reported as 0.
- Population summaries that include *P* values will report the *P* value to three decimal places with a leading zero (0.001). All *P* values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. *P* values <0.001 should be reported as <0.001 not 0.000.