Cetylite Industries, Inc.

1. STUDY PROTOCOL

Title:	A double-blind, partial cross-over, incomplete factorial study to assess the local anesthetic efficacy and safety of CTY-5339 Anesthetic Spray (CTY-5339-A) when applied to the cheek mucosal tissue in normal volunteers
Test Drugs:	CTY-5339-A (14.0% benzocaine, USP, 2.0% tetracaine HCL, USP) CTY-5339-CB (14.0% benzocaine, USP) CTY-5339-P (Vehicle Spray) (1 metered spray will deliver ≈200 µL containing either benzocaine 28 mg + tetracaine HCl 4 mg or benzocaine alone 28 mg or vehicle.)
Methods:	Single-center, randomized, double-blind, partial cross-over, incomplete factorial design. Pin Prick and QST Heat (QST) will be utilized to assess efficacy. Assessment of ECGs, pulse oximetry, and methemoglobinemia (blood co-oximetry) will be utilized to assess safety. ECGs and blood sampling will be performed at Baseline and after 1 hour of treatment. Pulse oximetry will be performed at Baseline and every 10 minutes through 1 hour after treatment.
Sponsor Name and Address:	Cetylite Industries, Inc. 9051 River Road Pennsauken, NJ 08110
Protocol Identification:	C-002
Development Phase IIb:	Proof-of-Concept Experimental Pain Model
Company/Sponsor Representative:	Stephen A. Cooper, D.M.D., Ph.D 117 Dalena Way Palm Beach Gardens, FL 33418 Phone: 973-710-6677
Compliance Statement:	The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and with standards of current Good Clinical Practice, as defined by

	the International Conference on Harmonization and all applicable FDA regulations.

Date	Version	Comment(s)	Author
April 20, 2016	2.0	Draft	S. Cooper
April 27, 2016	3.0	Draft- (Hersh, Weisman, Doyle)	S. Cooper
May 2, 2016	3.1	Draft- (Hersh, Weisman, Doyle)	S. Cooper
May 7, 2016	4.0	Draft- (Hersh, Weisman, Doyle, Riley, Phelps)	S. Cooper
May 7, 2016	4.1	Draft- (Hersh, Weisman, Doyle, Riley, Phelps)	S. Cooper
May 7, 2016	4.2	Draft- (Hersh, Weisman, Doyle, Riley, Phelps)	S. Cooper
May 10, 2016	4.3	Draft- (Hersh, Weisman, Doyle, Riley, Phelps)	S. Cooper
May 16, 2016	4.4	Draft- (Hersh, Weisman, Doyle, Riley, Phelps)	S. Cooper
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June 9, 2016	4.7	Minor Edits Prior to sign-off Final Version	S. Cooper/G.Doyle
August 8, 2016	5.0	Incorporation of Amendment 1 Changes/Edits	G. Doyle
October 17, 2016	6.0	Incorporation of Pulse Oximetry and Stopping Rules	S. Cooper/G. Doyle
October 18, 2016	7.0	Correct version with latest edits & Pulse Oximetry	S. Cooper/G. Doyle
October 19, 2016	8.0	Added FDA comment & IND Number	S. Cooper
October 19, 2016	9.0	Added Tegra comments	S. Cooper
November 3, 2016	10.0	Refinements to QST Assessment, other minor edits/corrections	S. Cooper/G. Doyle
November 4, 2016	10.1	Refinements to QST Assessment, other minor edits/corrections	S. Cooper/G. Doyle
November 8, 2016	10.2	Refinements to Baseline/Screening PPT and QST Assessments	S. Cooper/G. Doyle
November 9, 2016	10.3	Refinements to Baseline/Screening PPT and QST Assessments	S. Cooper/G. Doyle
November 10, 2016	10.4	Corrected Minor Inconsistencies	G. Doyle

Confidential Information

Signature Page

Investigator Signature

The signatures of the Principal Investigator (PI) and representatives of Cetylite Industries, Inc. (Cetylite) below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations, clinically and administratively, as detailed in the protocol, including all statements as to confidentiality. It is agreed that the conduct and results of this study will be kept confidential and that the CRFs and other pertinent data will become the property of Cetylite.

It is agreed that the protocol contains all necessary information required to conduct the study as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board or Independent Ethics Committee.

It is agreed that all participants in this study will provide written informed consent in accordance with the requirements specified in the FDA Regulations and the Current International Conference on Harmonization Good Clinical Practice Guidelines. All participants will also be informed that their medical records will be kept confidential except for review by representatives of Cetylite, Institutional Review Board or other University Offices, and the FDA and/or international regulatory authority.

The following have reviewed and approved this protocol:

Date

Principal Investigator's Name : Elliot Hersh, D.M.D., Ph.D.

Medical Monitor's Signature:	Date
Medical Monitor's Name: Stephen A. Cooper, D.M.D., Ph.D.	

Sponsor Representative's or President's Signature:	Date
Sponsor Representative's Name: Gary L. Wachman, President	

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Medical Monitor's Signature:	Date
_____	_____
Medical Monitor's Name: Stephen A. Cooper, D.M.D., Ph.D.	

Sponsor Representative's or President's Signature: Date

Sponsor Representative's Name: Gary L. Wachman, President

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3. CLINICAL PROTOCOL SYNOPSIS

TITLE:	A double-blind, partial cross-over, incomplete factorial study to assess the local anesthetic efficacy and safety of CTY-5339 Anesthetic Spray (CTY-5339-A) when applied to the cheek mucosal tissue in normal volunteers
STUDY NUMBER:	C-002
PRINCIPAL INVESTIGATOR:	Dr. Elliot V. Hersh, Director Clinical Pharmacology Research Unit, Dept. of Oral and Maxillofacial Surgery/Pharmacology, University of Pennsylvania, School of Dental Medicine
SITE:	University of Pennsylvania, School of Dental Medicine 240 South 40th Street, Robert Schattner Center, Philadelphia, PA 19104.
STUDY OBJECTIVES:	This study is designed to assess the efficacy and safety of locally applied CTY-5339 Anesthetic Spray compared to 14.0% benzocaine alone in normal volunteers using experimental sensation including pinprick with a needle (PPT) and heat sensation threshold (QST). The objective of this study is to demonstrate that the combination of the two constituents in the CTY-5339 Anesthetic Spray (CTY-5339-A) provides longer acting local anesthesia than 14.0% benzocaine alone (CTY-5339-CB). The primary objective is to demonstrate that the CTY-5339-A one-spray dose is superior to CTY-5339-CB. The secondary objective is to demonstrate that the CTY-5339-A up to two sprays is a safe dosage.
HYPOTHESIS:	CTY-5339-A when locally applied to cheek mucosal tissue in the mouth will have an onset comparable to the fastest constituent, benzocaine, and a prolonged effect comparable to the longest acting constituent, tetracaine, of the combination product. The study also is designed to demonstrate that both the CTY-5339-A one- and two-spray dosages are safe. (The assumption being made is that benzocaine has a faster onset of action than tetracaine.)

STUDY DESIGN:

This is a single-dose, partial cross-over, double-blind and single-center study with an active control treatment. All subjects will remain at the study center for each of the two 60 minute test sessions. The subjects will be tested at two different test sessions separated by 4-14 days.

The study will include 76 subjects who will be evaluated for 60 minutes at each test session. At each session, a circular area of approximately one inch in diameter will be isolated on one side of the inner cheek using an indelible oral pencil. Each session will use a different side of the cheek. The possible sequences of treatments with the metered spray at the two sessions are:

Session 1		Session 2	
Formulation	Sprays	Formulations	Sprays
CTY-5339-A	1	CTY-5339-CB	1
CTY-5339-A	2	CTY-5339-CB	1
CTY-5339-CB	1	CTY-5339-A	1
CTY-5339-CB	1	CTY-5339-A	2

To maintain double-blind conditions, the CTY-5339-CB subjects in the two spray sequences will also receive one spray with the vehicle control (CTY-5339-P). A third party not involved with evaluating subjects will administer the drug. The CTY-5339-P Vehicle will be sprayed outside the circumscribed area to avoid dilution of active drug. Efficacy evaluations will be done at 1-5 minute intervals beginning immediately after drug administration and will include:

Pin Prick (PPT) & QST Heat Sensation Tests:

For PPT, evaluations will be done at 1 minute intervals for the first 5 minutes to capture onset of anesthesia. Starting at 5 minutes after drug administration, both PPT and QST will be done at 5 minute intervals up to the one hour time point. If there is no indication of anesthesia by 10 minutes, the subject will be considered a treatment failure and the assessment of PPT and/or QST, as appropriate, will be discontinued. In addition, once onset of anesthesia has occurred, if there is no longer any anesthesia at two consecutive evaluation time points from 10 minutes onward, the assessment of PPT and/or QST, as appropriate, will be discontinued.

STUDY

Pin Prick Test (PPT): The PPT will be assessed, using a 90-mm, 26-

DESIGN: (cont)

gauge pencil-point spinal needle (Polymedic; Temena S.A., Bondy, France or equivalent). At screening, 3 pin pricks will be performed on each cheek. Pin pricks will be assessed using a 0 (no pain) to 10 (severe pain) Numerical Rating Scale (NRS). In order to be eligible for the study, for each cheek, subjects must have a minimum score of "3" for the last 2 pin pricks, and one of those scores has to be "4" or higher.

During each treatment session, at Baseline and at each post-dosing time point, 3 pin pricks will be performed first on the non-treated cheek and then on the treated cheek. At Baseline, pin pricks on both cheeks will be assessed using a 0 (no pain) to 10 (severe pain) NRS. Post-Baseline, pin pricks on the non-treated cheek will also be assessed using the 0 to 10 NRS, but on the treated cheek, the three repetitions will be compared to the non-treated cheek as "No pain", "Less Pain" or "Similar/More Pain". For each cheek, the first pin prick will not be used for analysis. Of the remaining 2 pin pricks, the one with the most severe pain rating will be used for analysis. During each treatment session, in order for a subject to be eligible to continue in the study, for each cheek, both of the last 2 Baseline assessment pin pricks must have a minimum score of "3" for the last 2 pin pricks, and one of those scores has to be "4" or higher. Post-Baseline, an assessment of "No Pain" or "Less Pain" at a drug application site will be recorded as presence of analgesia/anesthesia ("Responder").

Heat sensation threshold (QST-Heat): The heat stimuli are delivered in 3 repetitions, with inter-stimulus intervals of 30s. The basal thermode temperature is set at a comfortable 35ºC. The rate at which the thermode heats up is set at 0.5ºC/s, while the rate at which it cools down is set at 8ºC/s. The maximum thermode temperature is set at 51ºC. (Note: Hot beverages such as tea and coffee are frequently served at temperatures between 50^0C - 60^0C. Burns can occur at 65^0C.[25]). Heat sensation threshold will be defined as the temperature at which the subjects first feel tingling, warmth, heat, or pain.

At screening, QST-Heat assessments will be performed on each cheek. In order to be eligible for the study, for each cheek, subjects must have a mean Heat sensation threshold of 48.5ºC or less, based on the last 2 of the 3 readings.

During each treatment session, for each assessment, the first stimulus will be disregarded and the remaining two stimuli will be averaged for data analysis (unless the first two readings are 51^0C, in which case the third assessment will not be done). At Baseline and at each post treatment assessment, the heat sensation threshold will be performed on the treated cheek only. During each treatment session, in order for a subject to be eligible to continue in the study, subjects must have a

STUDY DESIGN: (cont)

mean Heat sensation threshold of 48.5°C or less, based on the last 2 of the 3 readings. Post-Baseline, the presence of analgesia/anesthesia will be defined when the heat sensation threshold at the treated site is higher than the Baseline ("Responder").

All tests on the treated cheek will be done near the center of the circumscribed area, but in a slightly different place at each consecutive evaluation time point. All tests on the non-treated cheek will be performed at approximately the same part of the cheek as those on treated cheek.

Randomization: A randomization code will determine the sequence of treatments and to which circumscribed area the treatment is administered (left or right cheek). Sensory testing will be done in the following order: pin prick followed, where applicable, immediately by heat sensation tolerance.

Subjects retain the right to withdraw from the study at any time.

EFFICACY MEASUREMENTS

The primary comparison of interest is one spray of CTY-5339-A compared to one spray of CTY-5339-CB. Co-primary efficacy variables are duration of effect as determined by PPT and duration of effect as measured by QST Heat. Duration of effect is defined as the time (in minutes) from onset to treatment failure (for PPT, treatment failure occurs when an assessment of "Same/More" pain, and for QST, a treatment failure occurs when the average heat temperature is the same or less than the average heat temperature at Baseline up to the 60-minute time point (at two consecutive time points).

The secondary efficacy variables include:

- Duration of anesthesia (PPT and QST Heat) for the two sprays of CTY-5339-A compared to one spray of CTY-5339-CB plus CTY-5339-P
- Duration of anesthesia (PPT and QST Heat) for the two sprays of CTY-5339-A compared to one spray of CTY-5339-A
- Onset of anesthesia for PPT and QST Heat
- Percentage of responders for PPT and QST Heat for both onset and duration
- Percentage of responders for PPT and QST Heat at each time point

OTHER MEASUREMENTS

At Baseline and at the end of the 60-minute test session an ECG, vital signs, and a 7 mL blood draw will be taken. The blood will be analyzed for the occurrence of subclinical methemoglobinemia by the HUP – Pepper Lab via co-oximetry analysis. At screening and throughout each test session, subjects will also be monitored with pulse oximetry. Methemoglobinemia is being defined as >5% of a subject's

hemoglobin in the methemoglobin state, or a pulse oximetry reading of less than 91%.

ESTIMATED DURATION OF SUBJECT PARTICIPATION IN THE STUDY:

The subjects will be tested on two separate occasions. Each session will take approximately two hours total time; however, the actual efficacy testing will take 60 minutes. There will be 4-14 days spacing between visits. A phone follow-up will occur 3 days (± 1 day) and 15 days (± 2 days) after the subject completes Sessions 1 and 2, respectively. If there are any adverse side effects, at the discretion of the PI, the subject may be asked to return to the study site for evaluation.

DURATION OF STUDY:

The study will be completed when the last subject completes the last follow up phone call. The expectation is that the study will be completed within 4-6 months of the first subject entry.

NUMBER OF SUBJECTS:

Up to 150 male and female subjects will be screened in order to enroll up to 76 ASA Category I or II subjects. The total number of exposures to study medication will be 152 (76 subjects x 2 exposures). Each of the CTY-5339-A treatment regimens will have 38 exposures and the CTY-5339-CB will have 76 exposures.

SAMPLE SIZE DETERMINATION:

The sample size was selected based on evaluating a reasonable number of subjects to determine whether CTY-5339-A has a longer duration of action than CTY-5339-CB, which contains 14.0% benzocaine only.

DOSAGE:

(specific gravity is slightly less than 1; therefore 200 uL is an approximate volume.)

CTY-5339-A 1-metered spay = 200 mg total (≈200 µL)
Benzocaine 28 mg + Tetracaine HCl 4 mg

CTY-5339-A 2-metered spays = 400 mg total (≈400 µL)
Benzocaine 56 mg + Tetracaine HCl 8 mg

CTY-5339-CB = 200 mg (≈200 µL)
Benzocaine 28 mg

INCLUSION CRITERIA:

a. Male and female subjects between 18-75 years of age with a Body Mass Index (BMI) ≤32;

b. Subjects are ASA Category I or II and are in good physical health as judged by physical and laboratory examinations;

c. Subjects with normal appearance of the oral mucosal tissues;

d. At screening and at Baseline during Session 1, subjects with PPT scores on both cheeks of at least "3" (on a 10 point NRS) on the last 2 of 3 readings, 1of which must be a score of at least "4";

e. Subjects with mean QST Heat sensation temperature assessments

on both cheeks of 48.5ºC or less based on the average of the last 2 of the 3 readings at screening or with a mean QST Heat sensation temperature assessment of 48.5ºC or less based on the average of the last 2 of the 3 readings on the treated cheek at Baseline during Session 1;

f. Subjects must agree to refrain from ingesting any systemic or topical analgesic medication for 3 days or 5 half-lives of the drug prior to and during each study session and alcohol for 1 day prior to and during each study session;

g. Subjects must agree to refrain from using mouth rinses, cough drops or throat lozenges on the day of each test session;

h. Female subjects must be physically incapable of childbearing potential (postmenopausal for more than 1 year or surgically sterile) or practicing an acceptable method of contraception (hormonal, barrier with spermicide, intrauterine device, vasectomized or same sex partner, or abstinence). Subjects using hormonal birth control must have been on a stable dose of treatment for at least 30 days and received at least 1 cycle of treatment prior to randomization. At Screening and at Baseline of both sessions, all females of childbearing potential must have a negative urine pregnancy test and not be breastfeeding;

i. Negative urine drug screen for drugs of abuse at Screening and at Baseline for each Study Session. A positive drug screen result may be permitted if the subject has been on a stable dose of an allowed medication for >30 days;

j. The subject is capable of reading, comprehending, and signing the informed consent form.

EXCLUSION CRITERIA:

a. Subjects with a history of any significant hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorders, including glaucoma, diabetes, emphysema, and chronic bronchitis;

b. Subjects with a history of any type of cancer other than skin related cancers;

c. Subjects with conditions that affect the absorption, metabolism, or passage of drugs out of the body, (e.g., sprue, celiac disease, Crohn's disease, colitis, or liver, kidney, or thyroid conditions);

d. Subjects with any history of alcohol or substance abuse (including a positive drug screen test);

e. Subjects that currently have or have a history of uncontrolled hypertension;

f. Subjects with a known hypersensitivity to any local anesthetic drug;

g. Subjects with a hematocrit level significantly below the normal range on the screening laboratory examination (as judged by the PI) or a pulse oximetry reading of less than 96% at screening or at Baseline of either session;

h. Subjects with any clinically significant abnormal lab result (as judged by the PI);

i. Subjects with any condition or history felt by the Investigator to place the subject at increased risk;

j. Subjects who have smoked or chewed tobacco-containing substances within 6 months prior to the start of the study;

k. Subjects judged by the Investigator to be unable or unwilling to comply with the requirements of the protocol;

l. Subjects who have used an investigational drug within 30 days prior to entering the study;

m. Subjects who have donated blood within 3 months prior to the start of the study;

n. Subjects who have previously participated in the trial;

o. Subjects who are members of the study site staff directly involved with the study or a relative of the Sponsor or other personnel involved with the study.

ECG TIMES: ECGs will be taken at screening, and during treatment visits at Baseline (Time 0, within 1 hour prior to drug administration) and then immediately after the 1 hour test session.

SAFETY EVALUATION: All potential subjects will receive a blood chemistry test and urine drug screen at the screening visit. As a safety precaution, at each study session, blood samples will be taken at Baseline and 1 hour after study medication to measure methemoglobin levels.

Pulse oximetry will be performed at screening, and at each session at Baseline, and 10, 20, 30, 40, 50 and 60 minutes after drug administration.

All the medications being evaluated in this study are marketed local anesthetic products in the United States and are being used within their currently indicated dosages and indications. Adverse experiences will be recorded as they occur during the treatment phase of the study and if voluntarily reported by the subject within 3 days following completion of the first study session and within 15 days following the end of the subject's participation in the study. Treatment-emergent AEs will be summarized by incidence. The events will be coded using the Medical

Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

Irritation and/or infection at the site of application will be assessed. The severity, relationship to treatment, action taken, and outcome of the events will be documented. The incidence of all adverse events and drug-related adverse events will be evaluated. In the event of any health related emergency, the clinical site will have a trained medical staff with a fully equipped emergency crash cart.

STATISTICAL ANALYSIS:

Primary Efficacy Endpoints:

- Duration of anesthesia as measured by PPT for one spray CTY-5339-A compared to the one spray CTY-5339-CB
- Duration of anesthesia as measured by QST Heat for one spray CTY-5339-A compared to the one spray CTY-5339-CB

Secondary Efficacy Endpoints:

- Duration of anesthesia as measured by PPT and QST Heat for the two spray CTY-5339-A compared to the one spray CTY-5339-CB plus one spray CTY-5339-P
- Duration of anesthesia as measured by PPT and QST Heat for the two spray CTY-5339-A compared to the one spray CTY-5339-A
- Onset of anesthesia for PPT and QST Heat
- Percentage of responders for PPT and QST Heat for both onset and duration
- Percentage of responders for PPT and QST Heat at each time point

Safety Data:

- SBP, DBP, and HR at Baseline and at the end of each 60-minute test session,
- Pulse oximetry at Baseline and at 10, 20, 30, 40, 50 and 60 minutes after drug administration,
- 12 Lead ECG at Baseline and at the end of each 60-minute test session,
- Methemoglobinemia at Baseline and at the end of each 60-minute test session, and
- Analysis of incidence and severity of all adverse events

For the PPT, a "Responder" is defined based on an assessment of "No Pain" or "Less Pain" in response to the pain stimulus at each observation time when compared to the non-treated site, (See Appendix 2). The % of responders at each time point will be compared between treatments. In addition, the % of subjects who have Onset (and Duration) will also be compared between treatments.

For the QST, a "Responder" is defined as follows: If the average heat

temperature at each time point is greater than the average heat temperature at Baseline, then the subject at that time point will be considered a "Responder". The % of responders at each time point will be compared between treatments. In addition, the % of subjects who have Onset (and Duration) will also be compared between treatments.

Data will be generated as the difference in response between the control, non-treated site and the active treatment site within in each subject.

ANOVA and pairwise t-tests will be used to compare CTY-5339-A treatment groups to the CTY-5339-CB treatment group.

4. STUDY FLOW CHART

TIME	Informed Consent	Medical History	Phys. Exam, ECG, Vital Signs, Pulse Ox	Lab Tests, Drug Screen	Pregnancy Test Females	Dosing	Pin Prick= P Heat Sensation Threshold= H (PPT & QST)	Blood Draw	AE Assessment
Screening	√	√	√	√	√		P (both cheeks), H (both cheeks)	√	√
Test Session 1		√	√	√*	√		P (both cheeks), H (treated cheek)	√	√
Test Session 2		√	√	√*	√		P (both cheeks), H (treated cheek)	√	√
-5 min									√
0 hr						√			√
1, 2, 3, 4 min							P (both cheeks)		√
5, 15, 25, 35, 45, 55 min							P (both cheeks), H (treated cheek)		√
10, 20, 30, 40, 50 min			√***				P (both cheeks), H (treated cheek)		√
60min			√				P (both cheeks), H (treated cheek)	√	√
Discharge									√
3 or 15-Day Call**									√

* Urine Drug Screen Only
**After Session 1, 3-Day Follow-up Call ± 1 day; After Session 2, 15-Day Follow-up Call ± 2 days
*** Pulse Oximetry Only, if <91%, the subject will be discontinued from the study

P=pinprick evaluation; H=heat tolerance evaluation

APPENDIX 1: DESCRIPTION OF TESTING METHODS

Appendix 1A: Pin Prick Test (PPT)

Oral Mucosa sensation directly over the circumscribed sites will be assessed with a 90-mm, 26-gauge pencil-point spinal needle (Polymedic; Temena S.A., Bondy, France or its equivalent) at Screening, Baseline and predetermined intervals after application of drug. To standardize the methodology, all tests are performed by holding the needle at its hub and orienting it perpendicular to the oral mucosa surface. Pressure is applied until the needle shaft bows slightly. At screening a numerical score on a 0 – 10 pain intensity scale (NRS) is recorded for each cheek. After study drug administration, subjects are instructed to rate the pinprick sensation perceived over the circumscribed treatment site compared to that perceived at the contra-lateral circumscribed, non-treated site and to report the sensation as none, less, or similar/more to the non-treated site. Reports of none or less indicate analgesia, while a report of similar/more indicates complete regression of analgesia. At each observation, 3 pin pricks are performed first on the non-treated side, and then on the treated side. For each cheek, the first pin prick will not used for analysis. Of the remaining two pin pricks, the one with the most severe pain rating will be used for the data analysis.

Appendix 1B: QST Heat Stimulus

1. This procedure uses the QST Heat Stimulator, a commercially available thermo-sensory analyzer (Medoc, 1 Ha'dekel, St. Ramat Yishai 30095, Israel) that delivers heat stimuli to the oral mucosa with a blunt thermode that is 6mm in diameter. A central unit generates and transmits the signal to the thermode. This signal is controlled by proprietary software stored on a laptop connected to the central unit. Also attached to the central unit is a hand-held control (a computer mouse) that allows a study subject to stop the heating of the thermode. As the temperature is increased, subjects are asked to report when they first start to feel a tingling, warmth, heat, or pain sensation. The subjects are instructed to turn off the heat probe by depressing the mouse when they first start to feel tingling, warmth, heat or pain. The heat is applied in graded increments until the subjects depress the mouse or the temperature reaches the maximum of 51ºC. At the maximum heat of 51^0 C, the probe automatically turns off and tissue is not damaged. (Note: Hot beverages such as tea and coffee are frequently served at temperatures between 50^0 C- 60^0C.[25])

2. The heat stimuli are delivered, in three repetitions, with inter-stimulus intervals of 30s. The basal thermode temperature is set at a comfortable 35ºC. The rate at which the thermode heats up is set at 0.5ºC/s, while the rate at which it cools down is set at 8ºC/s. The maximum thermode temperature is set at 51ºC. For each assessment, the first stimulus is discarded and the remaining stimuli are

averaged, unless the first two readings are 51ºC. In this case, the third assessment is not completed. At Baseline, and at each post-treatment time point, QST will be assessed on the treated cheek only.

APPENDIX 2: CRITERIA FOR A "RESPONDER"

PPT:

Based on "No Pain" or "Less Pain" response to the pain stimulus at each observation time when compared to the non-treated site, subjects will be classified as "Responders" or "Non Responders". At each observation, 3 pin pricks will be performed at each site (first on the non-treated cheek and then on the treated cheek). The first pin prick will not be used for analysis. Of the remaining two pin pricks, the one with the most severe pain rating will be used for the data analysis. If the most severe pain rating at that time point is "No Pain" or "Less Pain", then the subject at that time point is a "Responder".

QST:

The actual temperature data will be recorded at each time point. Temperatures will be recorded for "first sensation of tingling, warmth, heat, or pain". Scores will be censored at 51ºC, if no response is obtained. If the average heat sensation temperature at each time point is greater than the average heat sensation temperature at Baseline, then the subject at that time period will be considered a "Responder".

5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ANOVA	Analysis of variance
CFC	Chlorofluorocarbons
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CRF	Case Report Form
DESI	Drug Efficacy Study Implementation
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HCl	Hydrochloride
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NF	National Formulary
NRS	Numerical Rating Scale
PI	Principal Investigator
PK	Pharmacokinetics
PPT	Pin Prick Test
PT	Preferred Term
QST	Heat Stimulus Test
SAE	Serious Adverse Event
SOC	System Organs Class
TESS	Treatment Emergent Signs and Symptoms
USP	United States Pharmacopeia

6. ETHICS

6.1 Independent Ethics Committee or Institutional Review Board

This protocol, informed consent form, and any amendments, will be submitted to local ethics committees or institutional review boards (IRBs) for review and approval. A copy of the written approval or vote must be available and sent to the Sponsor before study initiation. Any amendment made to the approved protocol must be forwarded to and approved by the same ethics committees or IRBs before its implementation. Regulatory authority notifications will also be in place and fully documented prior to study start.

The Investigator and appropriate representatives from the Sponsor will sign the protocol to document their willingness to adhere to this protocol and to conduct the study in accordance with the FDA guidelines and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP).

6.2 Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and consistent with good clinical practice (GCP) as described by the United States Code of Federal Regulations (21CFR parts 50, 54, 56, and 312) and by the ICH Guidelines, effective 17 January 1997.

6.3 Subject Information and Consent

Written informed consent, in accordance with local clinical investigation regulations, must be obtained from the subject (subjects must be 18 years of age or older) prior to participation in the study. The Investigator must provide a description of the study medication (including any potential and possible hazards) and the study procedures to the study subjects. Information must be given both in oral and written form. The subject information provided will be in English, and may not include any language that appears to waive any of the subject's legal rights, or appears to release the Investigator, the Sponsor, the Sponsor's representative, or the institution, from liability or negligence.

The Investigator will provide the prospective subject sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence, and will discuss any questions the subjects may have. The Investigator will explain to the subject that withdrawal from the study is possible at any time without detriment to care. The Investigator will then ask the subject to give consent in writing.

The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the Sponsor, to the Sponsor's representative, to the FDA or other regulatory authorities. The informed consent will follow the FDA Regulations and ICH Guidelines, effective 17 January 1997.

7. INTRODUCTION

Cetylite Industries, Inc. (Cetylite) is a small pharmaceutical company based in Pennsauken, New Jersey. The primary product for this company is a local anesthetic spray, Cetacaine® Spray, consisting of a combination of the three active ingredients benzocaine hydrochloride (HCl), tetracaine HCl, and butamben, USP. The company also makes a liquid (solution) formulation with the same constituents (with the exception of a CFC propellant). The product has been grandfathered by the FDA under the DESI review and has been on the market in the US for approximately 60 years. The current indications for Cetacaine® are:

Cetacaine is a topical anesthetic indicated for the production of anesthesia of all accessible mucous membrane except the eyes. Cetacaine® Spray is indicated for use to control pain and gagging. Cetacaine® Spray is indicated to control pain and for use for surgical or endoscopic or other procedures in the ear, nose, mouth, pharynx, larynx, trachea, bronchi, and esophagus.

As a result of the Federal mandate to eliminate CFCs and under current Federal Regulations and exemptions, Cetylite has to reformulate the spray formulation once its supply of CFCs is exhausted (estimated to between 2020 and 2022). Since Cetacaine® is a grandfathered drug that never received an NDA approval; the FDA will now require an NDA for the reformulated product. As part of the recent communication with the FDA, Cetylite has agreed to remove butamben from the product and to reformulate a two-drug combination consisting of 14.0% benzocaine, USP and 2.0% tetracaine HCl, USP delivered without CFCs. The new product is a metered spray designated in this protocol as CTY-5339 Anesthetic Spray (CTY-5339-A).

In Cetylite's most recent correspondence with the FDA in April of 2014, Cetylite outlined its proposed program for the conversion of Cetacaine® Spray containing CFC propellant to a non-CFC containing spray. This letter outlined a proposed new alternate formulation, a proposed animal toxicology study and a clinical program. Since then the CTY-5339 formulation was developed without propellant as a metered dose pump spray. Cetylite has successfully completed a 28-day safety study in rabbits and will file the results of this safety study in their IND Application to initiate human clinical trials.

Summary of Critical Issues and Proposed FDA Questions

One of the key issues for Cetylite is how the development program translates to the final indications for CTY-5339 Anesthetic Spray. The primary use for CTY-5339-A is for the induction of local anesthesia of mucous membranes to suppress the gag reflex during intubation procedures. A secondary, but important, use is for anesthetizing buccal and gingival tissues.

Cetylite's proposed development program to the FDA consisted of the following:

- A 28-day rabbit study using nasal mucosa (completed in April 2016).
- A Phase II Cheek Mucosa study in normal volunteers- partial factorial design.
- A Phase III Nasal Intubation study in normal volunteers- full factorial design.

- A Phase III Gingival Surgery study in patients requiring gingival surgery- full factorial design.

Based on the successful completion of this program, Cetylite anticipates:

- Indications for use in the nose, throat and buccal cavity to suppress the gag reflex and pain sensation.
- Indications for use in all oral mucosa tissues for surgical procedures.

Cetylite's rationale for this development program is:

- Rabbit nasal mucosa is a highly sensitive and representative tissue type in human and provides an acceptable bridge to safety in other mucosal tissues, i.e. throat and buccal cavity.
- The Cheek Mucosa study will serve as the proof of concept study to evaluate the superiority of the combination in comparison to benzocaine alone.
- The Nasal Intubation study will serve as a representative of an airway model:
- The Gingival Surgery study is designed to demonstrate efficacy in a surgical model.

Table 1. Compositions of CTY-5339-A, the Benzocaine-Only Comparator (CTY-5339-CB) and the Vehicle Control (CTY-5339-P)

Ingredient	Grade	CTY-5339- (% w/w)		
		A[a]	CB[b]	P[c]
Benzocaine	USP	14.0	14.0	-
Tetracaine Hydrochloride	USP	2.0	-	-
Dehydrated Alcohol	USP	12.0	12.3	14.4
Polyethylene Glycol 300 (PEG 300)	NF	29.7	30.4	35.5
Propylene Glycol	USP	16.9	17.3	20.2
Purified Water	USP	18.0	18.4	21.5
Benzyl Alcohol	NF	5.0	5.1	6.0
Benzalkonium Chloride Solution (50%)	NF	0.5	0.5	0.5
Saccharin Sodium	USP	1.4	1.4	1.4
Artificial Banana Flavor	Food	0.5	0.5	0.5

[a] CTY-5339-A: Active formulation containing both 14.0% benzocaine, USP and 2.0% tetracaine hydrochloride, USP. Note: the term CTY-5339-A is used to designate the active formulation.
[b] CTY-5339-CB: comparator formulation containing benzocaine, USP
[c]CTY-5339-P: Vehicle formulation containing neither active ingredient

In the proposed human experimental Cheek Mucosal study in healthy volunteers, the CTY-5339-A or comparator CTY-5339-CB formulations will be sprayed onto a

circumscribed approximately one inch diameter area of the cheek. The area will then be tested with pin prick (PPT) and heat (QST) to assess onset and duration of effect. The maximal (total) dose of CTY-5339-A that a subject can receive during this study is 56 mg benzocaine and 8 mg tetracaine HCl. The expectation is that there will be very low systemic exposure of either benzocaine or tetracaine. The doses being used in this study are within the prescribed doses listed on the current Cetacaine® Spray label and are known to be safe doses of these local anesthetics.[1-24]

The dose of benzocaine and tetracaine being employed in this study are indicated doses on the Cetacaine® label. The PI has examined much higher exposures to benzocaine (80 mg – 200 mg) self-applied by patients to the oral mucous membranes and the offending tooth to treat toothache pain with relatively few minor adverse events recorded (no SAEs and no clinically discernible methemoglobinemia).[13] Likewise in the development of another product, the PI and his team have dosed subjects with 18 – 36 mg of tetracaine by the intranasal route to obtain maxillary tooth anesthesia with no SAEs reported (again this is 2 – 4 fold greater than the maximum tetracaine exposure on the current study.[8,10] These three studies were approved by the University of Pennsylvania IRB.

8. RATIONALE, OBJECTIVES, OUTCOMES, AND HYPOTHESIS

8.1 Rationale

The purpose of this study is to evaluate the onset and duration of analgesia in humans when CTY-5339-A is sprayed onto intact cheek mucosal tissue. If this proof-of-concept study is successful, then future studies will evaluate CTY-5339-A in intubation and gingival surgical settings.

8.2 Objectives

The objectives of this study are to evaluate the onset and duration of CTY-5339-A compared to benzocaine only spray (CTY-5339-CB) in a human experimental pain model.

8.3 Outcomes

8.3.1 Primary Outcome Measures

- Duration of anesthesia as measured by PPT for the one spray of CTY-5339-A compared to the one spray of CTY-5339-CB
- Duration of anesthesia as measured by QST Heat for the one spray of CTY-5339-A compared to the one spray of CTY-5339-CB

8.3.2 Secondary Outcome Measures

- Duration of anesthesia as measured by PPT and QST Heat for the two sprays of CTY-5339-A compared to the one spray of CTY-5339-CB plus one spray of CTY-5339-P

- Duration of anesthesia as measured by PPT and QST Heat for the two sprays of CTY-5339-A compared to the one spray of CTY-5339-A
- Onset of anesthesia for PPT and QST Heat
- Percentage of responders for PPT and QST Heat for both onset and duration
- Percentage of responders for PPT and QST Heat at each time point

8.4 Hypothesis

The following hypotheses will be tested to analyze the primary outcomes of the study:

- The null hypothesis that the duration of anesthesia (PPT and QST Heat) for the one spray CTY-5339-A group is the same as the corresponding duration for the CTY-5339-CB one spray group will be tested against the alternative hypothesis that the means are not equal.

The following hypotheses will be tested to analyze the secondary outcomes of the study:

- The null hypothesis that the duration of anesthesia (PPT and QST Heat) for the two spray CTY-5339-A group is the same as the corresponding duration for the CTY-5339-CB one spray plus CTY-5339-P one spray group will be tested against the alternative hypothesis that the means are not equal.
- The null hypothesis that the onset of anesthesia (PPT and QST Heat) for the CTY-5339-A groups is equal to the corresponding onset for CTY-5339-CB group will be tested against the alternative hypothesis that the means are not equal.
- The null hypothesis that the onset time until the first responder event (PPT and QST Heat) for the CTY-5339-A groups is equal to the corresponding onset time until a first responder event for CTY-5339-CB group will be tested against the alternative hypothesis that the event times are not equal.
- The null hypothesis that the duration time until the first non-responder event (QST and PPT) for the CTY-5339-A groups is equal to the corresponding duration time until the first non-responder event for CTY-5339-CB group will be tested against the alternative hypothesis that the event times are not equal.

The predicted outcome is that CTY-5339-A when locally applied to cheek mucosal tissue in the mouth will have an onset comparable to the fastest constituent, benzocaine, and a prolonged effect comparable to the longest acting constituent, tetracaine, of the combination product. The study also is designed to demonstrate that both the CTY-5339-A one and two-spray dosages are safe. (The assumption is made that benzocaine has a faster onset of action than tetracaine HCl.)

9. SUMMARY OF STUDY DESIGN

This is a single-dose, double-blind and single-center study with an active control treatment. All subjects will remain at the study center for each of the two 60 minute test sessions. The volunteer subjects will be tested at two different test sessions separated by 4-14 days and serve as their own control.

The study will include 76 subjects with 60-minute evaluations at each test session.

At each session, a circular area of approximately 1 inch in diameter will be isolated on one side of the cheek. Each session will use a different side of the cheek. The possible sequences of treatments at the two sessions are:

Session 1		Session 2	
Formulation	Sprays	Formulations	Sprays
CTY-5339-A	1	CTY-5339-CB	1
CTY-5339-A	2	CTY-5339-CB	1
CTY-5339-CB	1	CTY-5339-A	1
CTY-5339-CB	1	CTY-5339-A	2

(To maintain double-blind conditions, the CTY-5339-CB subjects in two spray sequences will also receive one spray with the vehicle control (CTY-5339-P) just outside the circumscribed area. A third party not involved with evaluating subjects will administer the drug.)

For PPT, evaluations will be done at 1-minute intervals following drug administration for the first 5 minutes to capture onset of anesthesia. Starting at 5 minutes after drug administration, both PPT and QST will be done at 5-minute intervals up to the one hour time point. Once onset has occurred, if there is no analgesia at two consecutive evaluation time points (from 10 minutes onward), the session will be discontinued. In addition, if onset of analgesia has not occurred by 10 minutes post dose, the subject will be considered a treatment failure and no further assessments will be made.

PPT: The PPT will be assessed, using a 90-mm, 26-gauge pencil-point spinal needle (Polymedic or equivalent; Temena S.A., Bondy, France or its equivalent). At each post dosing time point, PPT will be assessed in 3 repetitions on the non-treated site using a 0-10 Numerical Rating Scale (NRS) with “0” as no pain and “10” as severe pain. PPT will then be assessed in 3 repetitions on the treated site. These assessments will be compared to the contra-lateral, non-treated site as “No pain”, “Less Pain” or “Similar/More Pain”. “No Pain” or “Less Pain” at an application site will be recorded as presence of analgesia/anesthesia (“Responder”).

QST: The heat stimuli are delivered in 3 repetitions, with inter-stimulus intervals of 30s. The basal thermode temperature is set at a comfortable 35ºC. The rate at which the thermode heats up is set at 0.5ºC/s, while the rate at which it cools down is set at 8ºC/s. The maximum thermode temperature is set at 51ºC. The first stimulus is disregarded and the remaining two stimuli are averaged for data analysis. In situations where a maximal analgesia/anesthesia effect is demonstrated in the initial two repetitions, the QST test will not be repeated for the third repetition and the data will be recorded as maximal effect (51ºC) based on the first two repetitions.

Heat sensation threshold will be defined as the temperature at which the subjects first start to feel tingling, warmth, heat, or pain. All tests will be done near the center of the circumscribed area, but in a different place at each evaluation time point. For QST, the first time point after Baseline will begin at 5 minutes after drug administration. Subjects will have a hand held mouse that turns off the heat probe when they first start to feel tingling, warmth, heat, or pain. At the maximum heat level of 51^0 C, the heat probe turns off automatically. With a brief exposure at 51^0 C, there is no damage to the mucosal tissue.[25]

Randomization: A randomization code will determine in which circumscribed area each treatment is administered (left or right cheek). Immediately prior to beginning each 60 minute test session, both the contra-lateral cheek and the cheek to be dosed will be evaluated with the PPT. For QST, the screening assessments will be performed on both cheeks, while during each treatment Session, at Baseline and all post-dosing time points, assessments will be performed on the treated cheek only.

Subjects retain the right to withdraw from the study at any time.

The PPT and QST tests will be done near the center of each evaluation area but in a different place at each evaluation time point. For PPT, the non-treated control cheek will always be tested before the treated area. The testing will be done in the following order where applicable: PPT and then QST.

A safety phone follow-up call will occur 3 days (±1 day) after the Session 1 and 15 days (±2 days) following Session 2.

9.1 Number of Subjects

The study will include 76 completed subjects. It is anticipated that up to 150 ASA Category I and II subjects will be screened to obtain the 76 subjects needed for the study.

9.2 Inclusion Criteria

Individuals may be included in the study provided they meet all of the following inclusion criteria:

a. Male and female subjects between 18-75 years of age with a Body Mass Index (BMI) ≤32;

b. Subjects are ASA Category I or II and are in normal physical health as judged by physical and laboratory examinations;

c. Subjects with normal appearance of the oral mucosal tissues;

d. At screening and at Baseline during Session 1, subjects with PPT scores on both cheeks of at least "3" (on a 10 point NRS) on the last 2 of 3 readings, 1of which must be a score of at least "4";

e. Subjects with mean QST Heat sensation temperature assessments on both cheeks of 48.5^{o}C or less based on the average of the last 2 of the 3 readings at screening or with a mean QST Heat sensation temperature assessment of 48.5^{o}C or less based on the average of the last 2 of the 3 readings on the treated cheek at Baseline during Session 1;

f. Subjects must agree to refrain from ingesting any systemic or topical analgesic medication for 3 days or 5 half-lives of the drug prior to and during each study session and alcohol for 1 day prior to and during each study session;

g. Subjects must agree to refrain from using mouth rinses, cough drops or throat lozenges on the day of each test session;

h. Female subjects must be physically incapable of childbearing potential (postmenopausal for more than 1 year or surgically sterile) or practicing an acceptable method of contraception (hormonal, barrier with spermicide, intrauterine device, vasectomized or same sex partner, or abstinence). Subjects using hormonal birth control must have been on a stable dose of treatment for at least 30 days and received at least 1 cycle of treatment prior to randomization. At Screening and at Baseline of both sessions, all females of childbearing potential must have a negative urine pregnancy test and not be breastfeeding;

i. Negative urine drug screen for drugs of abuse at Screening and at Baseline for each treatment session. A positive drug screen result may be permitted if the subject has been on a stable dose of an allowed medication for >30 days;

j. The subject is capable reading, comprehending, and signing the informed consent form.

9.3 Exclusion Criteria

Individuals are not eligible for participation in the study if any of the following are noted:

a. Subjects with a history of any significant hepatic, renal, endocrine, cardiac, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorders, including glaucoma, diabetes, emphysema, and chronic bronchitis;

b. Subjects with a history of any type of cancer other than skin related cancers;

c. Subjects with conditions that affect the absorption, metabolism, or passage of drugs out of the body, (e.g., sprue, celiac disease, Crohn's disease, colitis, or liver, kidney, or thyroid conditions);

d. Subjects with any history of alcohol or substance abuse (including a positive drug screen test);
e. Subjects that currently have or have a history of uncontrolled hypertension;
f. Subjects with a known hypersensitivity to any local anesthetic drug;
g. Subjects with a hematocrit level significantly below the normal range on the screening laboratory examination (as judged by the PI) or a pulse oximetry reading of less than 96% at screening or at Baseline of either session;
h. Subjects with any clinically significant abnormal lab result (as judged by the PI);
i. Subjects with any condition or history felt by the Investigator to place the subject at increased risk;
j. Subjects who have smoked or chewed tobacco-containing substances within 6 months prior to the start of the study;
k. Subjects judged by the Investigator to be unable or unwilling to comply with the requirements of the protocol;
l. Subjects who have used an investigational drug within 30 days prior to entering the study;
m. Subjects who have donated blood within 3 months prior to the start of the study;
n. Subjects who have previously participated in the trial;
o. Subjects who are members of the study site staff directly involved with the study or a relative of the Sponsor or other personnel involved with the study.

10. CLINICAL SUPPLIES

10.1 Study Medication and Dosage

The Sponsor will supply the following study medication for administration:

Table 2. Study Medication

Treatment Group	Contents of Metered Spray Bottle
CTY-5339 Anesthetic Spray 1 spray (≈200 µL total)	14.0% Benzocaine, USP = 28 mg 2.0% Tetracaine Hydrochloride, USP = 4 mg
CTY-5339 Anesthetic Spray 2 spray (≈400 µL total)	14.0% Benzocaine, USP = 56 mg 2.0% Tetracaine Hydrochloride, USP = 8 mg
CTY-5339-CB 1 spray (≈200 µL total)	14.0% Benzocaine, USP = 28 mg
CTY-5339-P 1 spray (≈200 µL total)	Vehicle control (no active ingredient)

10.2 Packaging and Labeling

All study medication bottles will be labeled according to the FDA guidelines. In order to maintain the double-blind conditions for all treatment groups, the person(s) preparing and administering the test treatments will be different from the person(s) doing the clinical efficacy evaluations. A randomization list generated by the Statistics Group will list the investigational product(s) to be assigned to each subject during each treatment session, and which cheek (left or right) the study medication should be applied to. Subjects will be numbered starting from 101.

Study medication for subjects randomized to receive CTY-5339-A one spray in one treatment session and CTY-5339-CB one spray in the other treatment session will be double-blinded and packaged individually. Study medication for each subject will consist of 2 bottles, one bottle containing CTY-5339-A, and one bottle containing CTY-5339-CB. Each bottle will be labeled with the appropriate treatment session (A or B) and which cheek the study medication should be applied to (left or right), according the randomization schedule. The two bottles will be packaged in a box. Each bottle will be primed three times immediately prior to use.

Study medication for subjects randomized to receive CTY-5339-A two sprays in one treatment session and CTY-5339-CB one spray and CTY-5339-P one spray in the other treatment session will be packaged in bulk. The label for each bottle will contain the identity of its contents (CTY-5339-A, CTY-5339-CB, or CTY-5339-P). The person preparing and administering the test treatments will use the randomization list generated by the Statistics Group to apply the appropriate product to the appropriate cheek, and the appropriate area(s) of the cheek. The bottle will be primed three times prior to each use.

Another randomized listing generated by Statistics Group that has the same treatment assignments will be sent to the appropriate party responsible for packaging and labeling the study medications.

In addition, a master code will be kept by the Sponsor and at the study site. The study site master code will have individually sealed envelopes identifying the drug in each bottle for each patient enrolled in the study. The treatment for an individual subject may be unblinded in the event of an emergency and only if medically necessary without breaking the code for any other subject. Procedures to be followed for unblinding, notification responsibilities, and regulatory requirements are detailed in Section 12.4.5.

10.3 Assignment of Study Medication

Treatment assignments will be determined by a computer-generated randomization schedule maintained by the Statistics Group.

The randomization schedule will randomly assign one of the four treatments (CTY-5339-A one spray, CTY-5339-A two sprays, CTY-5339-CB one spray, or CTY-5339-CB one spray plus CTY-5339-P one spray) to the appropriate area(s) of the cheek mucosa. For PPT assessments, the untreated, control area on the contra-lateral side will always receive the stimulus assessment first.

Randomization numbers will be assigned in a sequential order starting from 101. A drug delivery team (different for the evaluators or other study personnel) will administer the treatments to the cheek mucosal area.

The randomization number assigned to the subject will be recorded in the CRF.

10.4 Administration of Study Medication and Duration of Evaluation

Each subject entered into the study will be given the randomly assigned study medications in the assigned circumscribed areas of the cheek mucosa at Baseline (Time = 0 hour). The duration of in-house treatment evaluations will last up to 60 minutes. The same team of coordinators and/or investigators will do all the evaluations.

10.5 Study Medication Accountability

10.5.1 Storage

All materials for this study must be stored in an area free from environmental extremes in a locked closet and with restricted access. A Cetylite representative will inspect the study medication storage area and discuss the study medication accountability system with the PI and site coordinators prior to shipment of the study medication to the site.

10.5.2 Study Medication Inventory

Upon receipt at the study site, the carton containing the study medication supplies will be stored unopened in the study medication storage room. At the study initiation, the PI or an appropriate designee, and a representative of Cetylite will conduct an inventory and complete the study medication inventory record. The original will be sent to Cetylite, and the PI will retain a copy. Any interim shipments will be inventoried by the PI or his/her designee. For all interim shipments, a study medication inventory record will be completed. The original will be returned to Cetylite, and the PI will retain a copy.

The PI or an appropriate designee, upon dispensing the study medication, must record the information on a study medication dispensing/return log. For accounting purposes and assessing subject compliance, a representative of Cetylite will review the study medication dispensing/return log, inventory the study medication, and inspect the storage facility at appropriate time intervals throughout the clinical investigation, depending on the length of the study. The PI must account for any discrepancy and/or deficiency.

10.5.3 Return of Study Supplies

All unused study medication shipped for this clinical trial will be returned to the Sponsor at the termination of the study. At the conclusion of the study, the PI or an appropriate designee, and a representative of Cetylite will inventory all used and unused study medication. The study medication inventory record for returned study medication will then be completed. Cetylite will retain the original, and the Investigator will retain a copy for his files.

All unused study medication will then be returned to:

Cetylite Industries, Inc.
9051 River Road
Pennsauken, NJ 08110
Attention: Returned Study Supplies
Protocol No. C-002

Upon receipt at Cetylite, a letter acknowledging the receipt of returned materials and a copy of the Study Medication Inventory Record will be sent to the Cetylite Medical Monitor.

11. STUDY PROCEDURES

11.1 Study Conditions

a. Only subjects who satisfy all inclusion and exclusion criteria and provide written informed consent may participate in the trial;

b. Subjects will remain at the study site for up to 2 hours at each of two test sessions.

c. Subjects will be tested in the same room and by the same coordinator team at each evaluation time point during both 1hour test sessions.

11.2 Schedule of Assessments

11.2.1 Screening Assessments

During the screening period, the PI or his designee will examine each subject and complete a checklist of the inclusion and exclusion criteria (see Sections 9.2 and 9.3, respectively) in order to determine the subject's eligibility. The Investigator or study coordinator will enter the pertinent historical information (including any medication taken recently) and clinical findings (including blood pressure) in the appropriate section(s) of the source documents.

A Subject Screening Log (provided by Cetylite) will be maintained in the site central file to document all subjects screened for entry into the study. Subjects will be screened only once. All subjects who meet the entrance criteria will provide written informed consent before participating in the study. Subjects are required to read, comprehend, and sign the informed consent. The screening procedure will also include evaluation of:

a. PPT and QST heat sensation assessments of each cheek

b. Vital signs (pulse rate and blood pressure in supine or reclining position, body temperature) and pulse oximetry (must be ≥ 96%)

c. Safety bloods including section Clinical chemistry (Sodium, Potassium, Creatinine, AST, ALT, Alkaline Phosphatase, LDH and Bilirubin), Hematology (Hemoglobin, Hematocrit, Thrombocytes, Erythrocytes and Full blood differential)

d. Urine drug screen and pregnancy test

e. 12 lead ECG (PR, QRS, QT interval, heart rate and rhythm)

Appropriate screening information for eligible subjects who are assigned a subject number and receive study medication will be transcribed onto the corresponding sections of the CRF. The experiment must occur within 30 days of the screening visit.

The following will be noted and recorded on the CRF:

- Date and time the drugs treatments were initiated and completed
- Any vital signs obtained (require blood pressure)

11.2.2 Baseline Assessments

After confirming continued eligibility, Baseline ECG, vital signs, and blood sample will be obtained. In addition, tissue site evaluations will be performed. The area of the treated cheek is circumscribed using an oral indelible pencil. Prior to drug administration, the presence or absence of pain after the PPT (using a 90-mm, 26-gauge pencil-point spinal needle), will be evaluated on both cheeks Heat sensation threshold (using QST) will be assessed in the circumcised area of the to-be-treated side of the cheek. These baseline data will be recorded on the CRF. The drug will then be administered onto the assigned circumscribed area. In order for a subject to be eligible to continue in the study, the last 2 of the 3 baseline PPT scores must be at least "3" or higher, and 1 must be "4" or higher. The mean of the last 2 of the 3 baseline temperature assessments must be 48.5^{o}C or less.

11.2.3 Post-Baseline Assessments

The time points of the post-baseline efficacy assessment are detailed in section 9 of this protocol. The PPT will be performed on both the control and treatment sites at each evaluation time point. The QST will be performed only at the treatment site for the post baseline evaluation time points.

11.3 Efficacy Assessments

11.3.1 Pin Prick Test (PPT)

Oral mucosal sensation directly over control and drug sites will be assessed with a 90-mm, 26-gauge pencil-point spinal needle (Polymedic; Temena S.A., Bondy, France or its equivalent) at Baseline and predetermined intervals after application of drug. To standardize the methodology, all tests are performed by holding the needle at its hub and orienting it perpendicular to the oral mucosa surface. Pressure is applied until the needle shaft bows slightly. For each test, the subject is instructed to rate the pinprick sensation perceived over the treatment sites compared to that perceived at the contra-lateral non-drug site, and to report the sensation as none, less, or similar/more to the treated site. Subjects will rate pain at the control site on a 0-10 Numerical Rating Scale with "0" as no pain and "10" as severe pain. Reports of none or less at the treatment site indicate analgesia, while a report of similar/more indicates complete regression or absence of analgesia.

At each observation, 3 pin pricks are performed at each site, first at the non-treated cheek and then at the treated cheek. The first pin prick is not used for analysis. Of the remaining 2 pin pricks, the one with the most severe pain rating is used for the data analysis.

11.3.2 Heat Sensation Tolerance

This procedure uses the QST Heat Stimulator, a commercially available thermo-sensory analyzer that delivers heat stimuli to the oral mucosa with a blunt thermode that is 6mm in diameter. A central unit generates and transmits the signal to the thermode. This signal is controlled by proprietary software stored on a laptop connected to the central unit. Also attached to the central unit is a hand-held control that allows a study subject to stop the heating of the thermode. The heat is applied in graded increments until the subject first reports either tingling, warmth, heat, or pain or the temperature reaches the maximum of 51ºC (Note: Hot beverages such as tea and coffee are frequently served at temperatures between 50^0C - 60^0C.[25])

The heat stimuli are delivered, in 3 repetitions, with inter-stimulus intervals of 30s. The basal thermode temperature is set at a comfortable 35ºC. The rate at which the thermode heats up is set at 0.5ºC/s, while the rate at which it cools down is set at 8ºC/s. The maximum thermode temperature is set at 51ºC. The first stimulus is discarded and the remaining 2 stimuli are then averaged (unless the first two stimuli reach the maximum of 51ºC). All tests will be done near the center of each circumscribed area, but in a different place at each evaluation time point.

11.4 Safety Assessments

Adverse events will be recorded when they are reported or observed. The AE collection period will begin at the time the subject is initially screened and continue for 15 days after the subject's last administration of study medication. Only the PI will determine the relationship to study medication for each AE prior to breaking the blind. The information will be recorded on the appropriate study center CRF and outpatient diary. In addition, vital signs (DBP, SBP, HR) will be assessed at the beginning and end of each 60 minute test session.

11.5 Blood Sampling, ECG and Pulse Oximetry

A blood sample (7 mL) will be taken at screening for purposes of assessing normal values for the subjects. Additional blood samples (7 mL each) will be taken at the beginning and end of each 60 minute test session to assess for the possible occurrence of subclinical methemoglobinemia. An ECG also will be performed both at Baseline and after the 60 minute sessions. All blood test analyses will be performed by the laboratory at Hospital of University of Pennsylvania-Pepper Lab. During each test session, subjects will also be monitored using pulse oximetry at Baseline and at 10, 20, 30, 40, 50 and 60 minutes. Methemoglobinemia is being defined as >5% of a subject's hemoglobin is in the methemoglobin state or a pulse oximetry reading is below 91%. The 5% level is still below the threshold where any clinically observable signs (blue lips,

chocolate-brown blood color or shortness of breath) would be seen. The study will be discontinued if a pulse oximetry reading falls below 91% or if the level of methemoglobinemia reaches > 5% in any subject.

11.6 Concomitant Medication

No other medications expected to confound the evaluation of the study medication will be allowed prior to or during the test sessions. This includes, but is not limited to, the use of any analgesics, oral rinses and mouth lozenges. All concomitant medications used during the study will be recorded in the CRF.

11.7 Study Participant Discontinuation

A subject will be considered discontinued from the study at any time under the following circumstances and will be replaced:

a. Any subject who violates any condition of the entrance criteria after having been entered into the study;

b. Any subject who develops a confounding concomitant illness (as determined by the subject, research coordinator or Investigator), serious adverse event, or a hypersensitivity to the study medication;

c. Any subject who becomes uncooperative, does not adhere to the requirements of the study protocol, or refuses to complete the study;

d. Any subject who requires any concomitant medication during the course of the study that could confound the study results;

e. Any subject who for the last 2 of the 3 assessments has PPT scores of less than "3" and does not have at least 1 assessment of "4" or greater, or has a QST mean heat sensation assessment higher than 48.5^{o}C based on the last 2 of the 3 assessments at Baseline prior to the start of each Session.

f. Any subject who has a methemoglobinemia (>5%) or a pulse oximetry reading below 91% during Session 1 or Session 2.

If necessary, additional coded study medication will be provided to the study site for replacement subjects. A representative of Cetylite will provide the replacement number to the study site.

Subjects who discontinue due to an adverse event will not be replaced. All discontinued subjects will record no further assessments after their time of discontinuation, and any recorded efficacy data will be included in the intent-to-treat (ITT) efficacy analysis but not in the evaluable subject analysis. All subjects taking study medication with follow-up safety data will be included in the safety analysis. Details of the reason(s) why a subject has been discontinued from the study should be recorded in the appropriate section of the CRF.

12. SAFETY

12.1 Subject Examinations

To ensure the safety and well-being of each subject entered into the study, the subject must first be examined by the PI or Sub-Investigator and medically cleared to participate as required by the protocol. Each subject will be observed for adverse events (AEs) and will be required to report any adverse events that develop during the course of the study and for 15 days post-drug treatment. If at any time during the study, the subject has a serious adverse event (SAE) or abnormality, the subject must be withdrawn from the study and appropriate care should be initiated.

12.2 Subject Safety Information

In accordance with the regulatory requirements regarding informed consent (21 CFR Part 50 Protection of Human Subjects), the subject will receive a copy of the informed consent form when discharged from the clinic. The informed consent form will include the information needed to contact the PI, along with a description of the study medication the subject may have received.

12.3 Availability of Investigator

Either the PI or an appropriate designee will be available to the subject at all times during the study and names and phone numbers of the PI and/or appropriate designee will be listed on the informed consent form.

12.4 Adverse Events

12.4.1 Definitions

Adverse Event

An adverse event (AE) will be defined as any untoward medical occurrence in a subject administered study medication. The adverse event does not necessarily have to have causal relationship with the study medication. An AE can therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, which is a change from baseline and is temporally associated with the use of the study medication, whether or not it is considered related to the study medication.

Severity

The following definitions will be used for grading severity of adverse events:

Mild - Either asymptomatic or subject is aware of the sign, symptom or event, but it is easily tolerated.

Moderate - Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe - Incapacitating with inability to do usual activities.

Causal Assessment

The causal relationship between an AE and the study medication will be determined by the PI on the basis of his clinical judgment and the following definitions:

- Associated: There is a reasonable possibility that the AE may have been caused by the study medication. This definition applies to those AEs that are considered definitely, probably, and possibly related to the use of the study medication.
    a. Definitely Related: An AE that: follows a reasonable temporal sequence from administration of the study medication; follows a known response pattern to the study medication; and, when appropriate to the protocol, is confirmed by improvement after stopping the study medication (positive de-challenge) and by reappearance of the reaction after repeat exposure (positive re-challenge); and cannot be reasonably explained by known characteristics of the subject's clinical state or by other therapies.
    b. Probably Related: An AE that: follows a reasonable temporal sequence from administration of the study medication; follows a known response pattern to the study medication; and, when appropriate to the protocol, is confirmed by improvement after de-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state or by other therapies.
    c. Possibly Related: An AE that: follows a reasonable temporal sequence from administration of the study medication and follows a known response pattern to the study medication but could have been produced by the subject's clinical state or by other therapies.
- Not Associated:
    a. Unlikely: An AE that does not follow a reasonable temporal relationship after administration of the study medication or could have been produced by the subject's clinical state or other therapies.
    b. Not related: An AE for which sufficient information exists to indicate that the etiology is unrelated to the study medication. Two or more of the following variables apply:
        - The AE does not follow a reasonable temporal sequence after administration of the study medication;
        - The AE is readily explained by the subject's clinical state or other therapies;
        - Negative de-challenge—the AE does not abate upon dose reduction or cessation of therapy (assuming that it is reasonable to expect abatement of the AE within the observed interval).

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that occurs at any dose and:

- Results in death;
- Is life threatening;
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect.
- Is a medically important condition: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, the event(s) may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.4.2 Reporting Adverse Events

Any SAE, regardless of causal relationship, must be reported immediately to the Medical Monitor at Cetylite no later than 24-hours after awareness of the SAE. Initial SAE reports may be made by telephone, and then followed by faxing a completed "Serious Adverse Event Form" and confirming by telephone that the fax was received. Compliance with this time requirement is essential so that Cetylite may comply with its regulatory obligations.

Contact:

Medical Monitor:

Name:	Stephen A. Cooper, D.M.D., Ph.D.
Address:	117 Dalena Way Palm Beach Gardens, FL 33410
Telephone:	973-710-6677
Fax:	Same

Follow up information relating to a serious adverse event must be reported to the Medical Monitor and to Cetylite within 24 hours of receipt by the PI by faxing a completed "Serious Adverse Event Form" to Cetylite and confirming by telephone that the fax was received. The subject will be observed and monitored carefully until the condition resolves or stabilizes and its cause is identified. The PI also will promptly notify the appropriate Institutional Review Board about the serious adverse event.

12.4.3 Other Reportable Events

The following events will be recorded and reported in the same time frame and following the same process as for serious adverse events:

- Overdose or abuse of the study medication with or without adverse events (for this protocol, a total daily dose of benzocaine exceeding 56 mg/day) or tetracaine exceeding 8 mg/day;
- Inadvertent or accidental exposure to the study medication with or without an adverse event.

12.4.4 Adverse Event Recording and Reporting

All AEs, whether serious or not, will be recorded on source documents and CRFs. The recording period for AEs and SAEs starts at the time the subject is screened**.** The recording period for both AEs and SAEs lasts through 15 days after the subject's last administration of study medication, regardless of the relationship to the study medication. The PI must follow up as medically necessary on all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in the case of permanent impairment, until the condition stabilizes.

For SAEs, the PI will provide all documentation pertaining to the event (*e.g.* additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the Cetylite Medical Monitor in a timely manner. Reports relative to the subject's course must be submitted to Cetylite until the event has subsided or, in the case or permanent impairment, until the condition stabilizes.

Information about all adverse events, serious and non-serious, including the event's severity, start and stop times/dates, chronicity, relatedness to study medication, and any actions taken, must be recorded on the appropriate CRFs. The information recorded will be based on the signs and symptoms detected during the physical examination and clinical evaluation of the subject as well as information recorded in the subject's diary, when applicable.

12.4.5 Breaking the Blind

A set of tamper-proof sealed individual envelopes containing the bottle numbers on the outside of the envelope and the treatment code inside the envelope, will be sent to the investigative site. In the event of a medical emergency that necessitates breaking the code, the sealed envelope containing the treatment code may be opened. The seal will only be broken by the Investigator in the event of an emergency for which knowledge of the subject's double-blind investigational product will have a direct impact on treatment decisions. Every effort will be made to discuss the decision to break the blind with the Cetylite Medical Monitor in advance.

When the blind is broken, the Investigator will notify the Sponsor's Medical Monitor immediately in order to document the reason and date of the unblinding. The event will also be recorded on the CRF and in the source document. The Investigator will submit a written explanation to the Sponsor describing the event within 5 business days.

12.4.6 Discontinuation of Study due to an SAE

The study will be discontinued for safety reasons if a serious adverse event occurs in one subject unless it is demonstrated that the serious adverse event is not related (as defined in section 12.4.1 of this protocol) to study drug, in which case the study will not be required to stop.

The IRB will be notified within 24 hours of any event that results in discontinuation of the study.

13. STATISTICAL METHODS AND DATA HANDLING

The Statistics Group will perform statistical analyses of efficacy data. All computations will be performed using SAS® version 9.1 or higher (SAS Institute, Cary, NC). Statistical significance will be declared if the p-value is ≤0.05.

Descriptive statistics for numerical variables will include n (number of subjects involved), mean, standard deviation, median, minimum, and maximum values. Categorical variables will be described by number and percent.

13.1 Sample Size Determination

This study is a proof-of-concept study to determine if CTY-5339-A one or two sprays have a relevant efficacy advantage over CTY-5339-CB. Although a statistically significant difference is desirable, a clear-cut trend for increased duration of analgesia would be acceptable. A sample of 76 subjects in the efficacy evaluation part was felt to be adequate for the purposes of this proof-of-concept study.

13.2 Analysis Populations

There will be three analysis populations:

Safety population: will include all randomized subjects who received the study medication. This population will be used for all safety summaries.

Intent-to-Treat (ITT) population: will include all randomized subjects who dosed with study medication and provided a Baseline assessment. All secondary efficacy analyses and summaries will be performed using this population.

Modified Intent-to-Treat (mITT) population: will include all randomized subjects who, as documented prior to the breaking of the study blind: (1) met all the inclusion and exclusion criteria and; (2) either completed the two 60 minute test sessions or returned to baseline values in all the evaluation tests. The primary efficacy analyses will be performed using this population.

13.3 Demographic Data and Baseline Comparability

Quantitative demographic data will be described by summary statistics (number of subjects, mean, standard deviation, median and range). The number and percentage of subjects will be presented for categorical variables. No formal statistical comparison

between the treatment groups will be performed. Demographic data summary will include age, gender and race. These data will be presented for the overall safety population only, unless the sample sizes for ITT and mITT subject populations are very different from that of safety population (differ by more than 3 subjects). In this case, demographic data will be presented for that population. Baseline efficacy assessments will also be presented by treatment group.

13.4 Data Adjustments and Derived Endpoints

13.4.1 Time Windows

Because some subjects may complete their assessments at times differing from the scheduled times, each such score will be adjusted so as to reflect more accurately the score that would have been observed had it been recorded at the scheduled time. With the exception of the 1-5 minute PPT evaluations, time windows will be created for each of the 5-minute scheduled PPT time points, the widths being ±3 minutes. The time window for the 1-5 minute PPT evaluations will be ±30 seconds.

- If an assessment is performed within a time point window, the corresponding value will be assigned to that time point (*e.g.,* an assessment performed anywhere between 3 and 7 minutes from the previous evaluation, regardless of when it was scheduled, will be assigned to the scheduled 5 minute time point).

If a particular time point has no value within its window, then the PPT or QST Heat value with be assigned using either Last Observation Carried Forward (LOCF) or Next Observation Carried Backward (NOCB). In particular, LOCF will be used for missing data prior to onset, and NOCB will be used for missing data after onset to conservatively estimate both onset and duration.

13.5 Statistical Methods for Efficacy Evaluations

The primary efficacy analyses will be based on Modified Intent-to-Treat Population. The key comparisons will include:

1. CTY-5339-A, one spray versus CTY-5339-CB, one spray

The co-primary efficacy variables are duration of effect as measured by PPT and QST Heat. Duration of effect is defined as the time (in minutes) from onset to treatment failure (i.e., for PPT, an assessment of “Same/More” pain, and for QST, the average heat temperature is greater than the average heat temperature at Baseline (non-treated cheek), up to the 60-minute time point (at two consecutive time points). For those discontinuing from the study for any other reason, the time to treatment failure will be censored at the last assessment time.

The secondary efficacy variables include:

- Duration of effect (PPT and QST) for CTY-5339A two sprays versus CTY-5339-CB, one spray plus CTY-5339-P one spray

- Duration of effect (PPT and QST) for CTY-5339A two sprays versus CTY-5339-A one spray
- Onset of anesthesia in minutes for PPT and QST Heat
- Percentage of responders at each time point for PPT and QST Heat for both onset and duration

Continuous variables will be analyzed via an ANOVA model with treatment effects at each of assessed time points. Pairwise comparisons for variables related to percentages will be analyzed via chi square tests. The 95% confidence intervals of the treatment differences will be presented using normal approximation with continuity correction, if appropriate. Pairwise comparisons for time-to-event related variables will be analyzed via a log rank model with treatment effects. Median time to event will be estimated and the 95% confidence intervals for the median will be presented, if appropriate.

13.6 Multiple End Points and Multiple Comparisons

Duration of Effect, as assessed by PPT and QST Heat are co-primary efficacy parameters. In order to control the overall significance level for the two primary endpoints, the total alpha level of 0.1 is Bonferroni adjusted to 0.10/2 = 0.05 (since this is a proof of concept study, the total alpha level of 0.1 instead of 0.05 has been selected). The study will be considered successful if either of the two primary endpoints is statistically significant.

13.7 Safety Analysis

The safety population will consist of all subjects who received the study medication and had follow up data.

Adverse event (AE) analyses will include all AEs which initially occurred, or worsened following treatment (*i.e.,* treatment emergent signs and symptoms, TESS). AEs will be summarized by the MedDRA preferred term and by system organ class and classified according to their severity (mild, moderate, or severe) and relationship ("Suspect" or "Not Suspect") to study medication. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study medication, the AE will be classified according to the worst relationship.

ECG data will be summarized and presented based on assessment category ("Normal", "Abnormal, but not clinically significant" or "Abnormal, clinically significant") by treatment group. Changes in SBP, DBP, and methemoglobinemia rate from Baseline to 60 minutes will be summarized by treatment group. Pulse oximetry will be summarized at each time point by treatment group.

14. STUDY ADMINISTRATION

14.1 Investigator Study Binder

The Sponsor will supply to the PI an Investigator Study Binder that must be maintained at the study site, unless an alternative filing system is deemed appropriate by the Cetylite representative.

Included in this binder will be tabbed sections for maintaining the following: study identification and study site staff signature list, monitoring visit record, protocol and amendments/administrative changes, curricula vitae, Institutional Review Board documentation, informed consent form, product receipt and accountability forms, correspondence, subject screening record, and master subject log. This binder must be kept current and be available for review by representatives of the Sponsor and any official regulatory body.

14.2 Subject Identification

For purposes of confidentiality and to maintain anonymity, subjects will be assigned identification numbers. Subjects will be numbered sequentially as they enter the study. Once subjects meet the entry criteria, they will be assigned a randomization number corresponding to study medication. Subjects should be identified to the Sponsor only by their assigned number, initials and date of birth. The PI or his designee will maintain a complete list of all subjects enrolled in the study with their current mailing address on the master subject log. This list is necessary should contact of subjects be required in the future.

14.3 Case Report Forms

Case report forms (CRFs) provided by Cetylite will be used to document all subject data and will be typed or printed legibly in black or blue ink. Prior to submission to Cetylite the PI will review all CRFs and sign where necessary. It is important that the CRFs be completed in a timely manner for each subject evaluation in order that the progress and results of the study may be closely followed by the Sponsor. Corrections to CRFs must not obscure the original entry; a single line through the original entry is sufficient. All corrections must be initialed and dated by the responsible individual.

CRFs are to be completed and held for retrieval by a representative of Cetylite, unless otherwise directed. All study records must be retained in accordance with Section 14.10. A study site may use forms of their own design, following approval of the form by Cetylite, as source documents only.

14.4 Monitoring of Study

The study will be monitored by representatives of Cetylite. On-site visits will be made before the study begins, at regular intervals during the conduct of the study, and at the completion of the study. Communication by telephone, mail, and facsimile may also be used to supplement on-site visits.

The representative of Cetylite will inspect all CRFs and corresponding portions of the subject's original office and/or hospital records. These inspections are for the purpose of

verifying adherence to the protocol and determining the completeness and exactness of the data entered on the CRF and study medication log.

As a part of monitoring and inspection of this study, the PI agrees that Cetylite, its employees or representatives, Institutional Review Board or Independent Ethics Committee, as well as representatives of the FDA will have the right to inspect and review pertinent medical records relating to this trial. In addition, informed consent documents signed by study participants will indicate approval to release their medical records for review while maintaining their confidentiality.

14.5 Protocol Modifications

As the study progresses, any necessary additions or changes to the protocol will be decided by mutual agreement of the PI and the Clinical/Medical Monitor. An amendment to this effect will be submitted first to Cetylite for review and approval and then to the Institutional Review Board for review and approval prior to implementation. If the protocol change impacts the conduct of the study, the informed consent form will be amended, as appropriate. A protocol change to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the reviewing Institutional Review Board is notified in accordance with 21 CFR 56.104(c). Otherwise, no deviations will be permitted. Approved amendments will become part of the protocol and will be reported to the appropriate regulatory authority prior to implementation.

14.6 Discontinuation of Study by Sponsor or PI

Cetylite reserves the right to discontinue the study for administrative reasons at any time. All study medication and CRFs will then be returned to the Sponsor.

If the PI discontinues the study prematurely, the PI will return all study medication and CRFs to the Sponsor and provide a written explanation as to why the study was ended.

14.7 Disclosure of Data/Publications

All information obtained during the conduct of the study will be regarded as confidential. Agreement from Cetylite must be obtained prior to disclosing any information relative to the study.

Upon completion of the study, Cetylite may decide to publish the results with the PI in a recognized scientific journal and/or present the results (as a poster or oral presentation) at a meeting of a recognized scientific association. In order to safeguard against disclosure of confidential information, however, Cetylite requires that it has the right to review any manuscript and/or abstract prior to submission. A draft manuscript must be reviewed by Cetylite 60 days prior to submission of the final version to the journal. Abstracts of presentations must be reviewed by Cetylite 15 days prior to submission. Cetylite assures the PI that all manuscripts and abstracts will be reviewed promptly.

14.8 Informed Consent

Regulations require that written informed consent must be obtained for each subject prior to entry into the study. Informed consent means the knowing consent of an individual, so

situated so as to exercise free power of choice without undue inducement or constraint or coercion. The informed consent form will include all elements required by the FDA. A copy of the consent form will be provided to the subject.

The Investigator will provide Cetylite with a copy of the consent form as approved by the Institutional Review Board at University of Pennsylvania.

The PI will ensure that this study is in full conformance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong South Africa and Scotland) as well as GCP and ICH guidelines.

14.9 Institutional Review

Prior to initiating the study, the protocol and amendments, informed consent form, any advertisement, PI's and sub-investigators' curriculum vitae, and investigational product brochure must be reviewed and approved by a properly constituted Institutional Review Board as required by the FDA and the International Conference on Harmonization Guidelines.

The PI must certify to Cetylite that the Institutional Review Board meets all the legal requirements as specified by the FDA. The Institutional Review Board must provide a signed and dated statement that the protocol, informed consent form, and other pertinent documents, such as recruitment advertisements (in any medium) have been approved by the Committee. If the study continues longer than one year, re-approval must be obtained from the Institutional Review Board on an annual basis. The Institutional Review Board must be informed of any changes in research activity including amendments to the protocol and/or informed consent form, advertisements, and serious adverse events.

At the conclusion of the study, the PI must submit a summary of the study to the Institutional Review Board with a copy forwarded to Cetylite no later than 60 days after the study closeout visit.

14.10 Retention of Records

International Conference on Harmonization (ICH) and FDA regulations require that all study records be kept in the files of the PI for two years following the date a marketing application is approved for the indication which was investigated, or if no application is filed or if the application is withdrawn, two years after the investigation is discontinued and the regulatory authority is notified. Additionally, the master subject log must be maintained for a minimum period of 10 years from the dates defined above. Cetylite will notify the PI of the above date. No study documents may be destroyed or moved to a new location without prior written approval from Cetylite.

If at any time the PI is no longer able to maintain the required study records, or if the PI relocates or delegates custody of the records to another, Cetylite must be notified in writing as soon as possible. In any case, Cetylite retains the right to reclaim all study records. If Cetylite reclaims the study records, the master subject log, which contains confidential information identifying and how to contact the study subjects, will be provided to Cetylite in a sealed envelope labeled "confidential".

The PI assumes the responsibility of retaining the following records:

a. Signed and dated protocol and amendments, written authorization to allow enrollment of potentially ineligible subjects or otherwise amend the protocol;

b. Curriculum vitae of the Principal Investigator and sub-investigators;

c. Investigational Product Brochure or full prescribing information, instructions to Principal Investigator, or other information provided by Cetylite for conducting the clinical study;

d. Records of receipt and disposition of all product supplies, including:

- Dates and amounts of product received from Cetylite
- Lot numbers or other identification
- Dates and quantity dispensed and returned for each subject
- Dates and amounts of product returned to Cetylite

e. Institutional Review Board approval, correspondence, interim reports, and final study summary;

f. Documented informed consent for each subject

g. Completed CRFs and diaries (if applicable) for each subject including all source documents from which the CRFs were prepared

h. Subject screening record indicating disposition of each subject and reason for exclusion when appropriate

i. Master subject log indicating all subjects enrolled in the study with their current mailing address

j. Detailed medical histories for each subject containing medical history prior to enrollment with basic identifying information linking records to CRFs, results of all diagnoses made, therapy provided, any other data on subject's physical state

k. Medical history during the study including documentation of enrollment, concomitant or concurrently administered therapy, observations on subject's condition during the study, any factors that might alter the effects of the test product, adverse event or laboratory abnormality reports and follow-up where appropriate

l. Copies of tests and/or examinations results required by the protocol, including laboratory normal values and accreditation, if applicable

m. Copies of interim and final reports issued to the Institutional Review Board or Cetylite

n. Documentation of contacts between Cetylite and the PI and/or other study site personnel, including all correspondence

o. Copies of any reports on serious adverse events, death, or life-threatening symptoms

p. Roster of all study personnel with their signatures and signed initials

q. Monitoring visit record

14.11 Responsibilities of Principal Investigator

In agreeing to conduct this study, the PI assumes certain responsibilities mandated by FDA regulations: an Investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan as defined by the protocol, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of the products under investigation. An Investigator will, in accordance with the appropriate regulations, obtain the informed consent of each human subject to whom the product is administered. The Investigator will retain all study documents as stipulated in Section 14.10. The Investigator certifies that he/she has not been disbarred by any regulatory agency from conducting clinical trials. The Investigator will comply with the requirements outlined in the CFR final ruling, Financial Disclosure by Clinical Investigators, effective February 2, 1999.

14.12 Filing of Protocol with FDA

This protocol and data from this study may be subsequently filed with the U.S. FDA.

15. TEXT REFERENCES

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