ABSOLUTE BIOAVAILABILITY/PHARMACOKINETIC AND RESIDUAL DRUG ANALYSIS OF TOPICAL LIDOCAINE SYSTEMs IN HEALTHY ADULTS

Short title: Lidocaine Release from Topical Patches in Healthy Adults

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Sponsor:
Food and Drug Administration

Grant Number:5U01FD004275-03

NCT03310970

Version 1.0
9/6/17

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and the applicable Food and Drug Administration (FDA) and other Department of Health and Human Services regulatory requirements. All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Clinical Principal Investigator: Ken-ichi Ueda, MD
(*Medically Accountable Investigator*)

Signed: _____ **Date:** _____

U01 Principal Investigator: Nicole K. Brogden, PharmD, PhD (contact)

Signed: _____ **Date:** _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AUC	Area Under the Serum-Concentration Curve
C_{max}	Maximum Serum Concentration
C_{ss}	Steady State Concentrations
CFR	Code of Federal Regulations
CL	Clearance
CNS	Central Nervous System
CRF	Case Report Form
CRU	Clinical Research Unit
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICTS	Institute for Clinical and Translational Science
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	Intravenous
K_{el}	Elimination Rate Constant
MAI	Medically Accountable Investigator (i.e., licensed clinician)
NBP	Noninvasive Blood Pressure
PI	Principal Investigator
PK	Pharmacokinetics
PSI	Primary Skin Irritation
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
QMP	Quality Management Plan
RIHSC	Research Involving Human Subjects Committee
RLD	Reference Listed Drug
SAE	Serious Adverse Event/Serious Adverse Experience
SpO_2	Oxygen Saturation
T_{max}	Time of Maximum Serum Concentration
UI	University of Iowa
UICOP	University of Iowa College of Pharmacy
UIHC	University of Iowa Hospitals and Clinics
US	United States
V	Volume of Distribution

PROTOCOL SUMMARY

Title:	Absolute Bioavailability/Pharmacokinetic and Residual Drug Analysis of the Lidoderm® System in Healthy Adults
Population:	Healthy, non-smoking adults aged 18-65 years
Number of Sites:	Single site: University of Iowa College of Pharmacy/ University of Iowa Hospitals and Clinics
Study Duration:	Approximately up to 12 months
Subject Participation Duration:	Approximately 3-4 weeks, including the screening period
Description of Study Products:	Lidoderm® patch 5% (Endo Pharmaceuticals Inc.); lidocaine patch 5% (Mylan), lidocaine hydrochloride 20 mg/1 ml preservative free single dose vials (Auromedics Pharma LLC)
Objective:	To determine the rate of lidocaine delivery after using a reference (Lidoderm®) topical drug delivery system in healthy adult volunteers.
Description of Study Design:	This will be a three arm, open-label, crossover clinical pharmacokinetic study; the three arms will include administration of intravenous (IV) lidocaine hydrochloride, topical administration of a single strength of the reference listed drug (RLD) Lidoderm® 5% topical patch manufactured by Endo Pharmaceuticals, and topical administration of a single strength lidocaine 5% patch manufactured by Mylan. A) Pharmacokinetic Determination of Strength The study will be a three arm, open-label, crossover clinical pharmacokinetic study (n=24 healthy adult subjects, or statistically suitable number) with a minimum 48 hour washout period between each study arm. Each subject will be his/her own control. The study products are: • Lidoderm® 5% patch (Endo Pharmaceuticals Inc.) • Lidocaine 5% patch (Mylan) • Lidocaine hydrochloride 20 mg/1 ml preservative free single dose vials (Auromedics Pharma LLC) Blood samples will be obtained as follows (based on administration route):

	• Patch studies: 60 min pre-application, during the 12 hour patch wear, and up to 48 hour post patch application • 60 min pre-IV injection and then up to 10 hour post IV injection B) Residual Drug Analysis Determination of Strength In conjunction with the above described pharmacokinetic study, residual drug analysis will also be conducted for the lidocaine patches. • The worn patches are retained for drug content analysis. • Upon removal of the product after prescribed wear period, the skin (at site of application) is swabbed and the swabs are retained for drug content analysis

1. KEY ROLES

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

There are numerous topical and transdermal drug delivery systems that are currently available in the United States; the first transdermal delivery system (Transderm Scōp®) was approved by the Food and Drug Administration (FDA) in 1979. Drug delivery systems in the form of patches are convenient, attractive, and easy to use. Lidocaine is a very popular topical patch available on the US market today, used for local relief of pain associated with post-herpetic neuralgia.

Accurate determination of the rate and extent of drug release and absorption is crucial to ensure the safety of individuals using drug patches. Delivery rate and extent can be determined early in the development process by using *in vitro* skin flux permeation studies, the extent of absorption can be determined in humans by accurately quantifying residual drug from patches post-wear, and the delivery rate can be determined in pharmacokinetic studies. In this proposal, we will employ two types of evaluation to determine the rate and extent of drug release and absorption from two lidocaine patch products: residual drug analysis post-wear and pharmacokinetic analysis in healthy adult volunteers. In addition, we will compare the serum drug concentrations following patch and intravenous (IV) administration, in order to determine the absolute bioavailability of the patches. We will conduct residual drug analysis of the patches following *in vivo* wear using highly sensitive validated quantification methods. Positive outcomes of this project will identify appropriate methods to determine the rate and extent of drug release and absorption from topical drug patches, and will help regulatory agencies in the development of Guidances for Industry regarding the characterization of drug release and absorption kinetics to ensure the safety of individuals utilizing these types of products.

2.2. Rationale

The rationale of this study is to determine the absolute bioavailability and pharmacokinetics of topical lidocaine through development of an appropriately controlled and well-characterized methodology to quantify the exposure of healthy adults to lidocaine during wear, so that the rate of drug release and delivery can be defined in a manner that can help the regulatory agency (FDA) in developing Guidances for Industry regarding the characterization of drug release and absorption kinetics to ensure the safety of individuals utilizing these types of products.

The project involves crossover pharmacokinetic (PK) studies using two lidocaine topical patch products made by different manufacturers, and IV injection of the corresponding drug (e.g. lidocaine hydrochloride). The IV data will be utilized to determine clearance (CL) of the drug from the systemic circulation. Different mathematical approaches including, but not limited to, deconvolution will then be utilized to determine the rate of drug delivery from the patch into the systemic circulation using PK parameters derived from non-compartmental and/or compartmental analyses of lidocaine serum concentrations measured using sensitive, validated bioanalytical methods. In order to compare the data obtained from this study to previously published data, a similar time course was selected for collecting the blood samples for serum analysis. As part of this study, appropriate methodologies will also be developed to precisely characterize the (residual) drug content in the selected products. Following the *in vivo* studies, residual drug content of the worn patches will be determined to calculate exposure from the patch (i.e. quantifying the amount of drug delivered *in vivo* over time based upon residual drug analysis data).

Since this will be a crossover study, all subjects will complete all three study arms. One of the patch systems will be applied first, followed by at least 48 hours of washout period. Then the IV injection will be administered followed by at least 48 hours of washout period. Last, the second patch system will be applied. Subjects will be assigned to one of two groups. Regardless of group, all subjects will receive the treatments in the same order of patch-IV-patch. In Group 1 the patch manufactured by Mylan will be applied first; in Group 2 the patch manufactured by Endo Pharmaceuticals will be applied first.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

Lidocaine topical patches:

Topical lidocaine 5% patches are approved by FDA for use in the United States and have been used for many years; the likelihood of unexpected frequent side effects is minimal. The major risks associated with topical lidocaine administration are reactions locally at site of patch application, including blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or abnormal sensation. The dose absorbed from the topical patches is small and so systemic adverse events are relatively unlikely. Systemic adverse effects, when they do occur, are expected to be similar in nature to those seen with other amide local anesthetic agents. This includes symptoms of central nervous system (CNS) excitation and/or depression, such as: light headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremor, convulsions, unconsciousness, respiratory depression, and arrest. Adverse events manifesting in the cardiovascular system may include bradycardia, hypotension, and cardiovascular collapse leading to arrest. Other miscellaneous adverse events that have been reported but causality has not been established include the following: asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, nausea, nervousness, exacerbation of pain, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

The study has been designed to reduce these potential risks as follows. According to the FDA approved dosing, up to three patches may be applied once for up to 12 hours, in a 24 hour period. Thus, the proposed dosing regimen in this study is three patches, applied to the lower back. The skin will be carefully inspected prior to patch application and patches will not be applied to skin that is irritated or compromised in any way. The patches will be removed at the end of the approved 12-hour wear period. This dosing regimen will be used for both types of patches studied. The mean peak plasma concentrations obtained from this dosing regimen is expected to be approximately 0.13 μg/ml, which is ~$1/10^{th}$ of the concentration required for treatment of cardiac arrhythmias (0.4 ± 6.0 μg/mL are considered therapeutic for treatment of cardiac arrhythmias)[1].

Lidocaine hydrochloride IV injection:

The major risks associated with the use of lidocaine hydrochloride IV injection include CNS effects and cardiovascular effects. CNS reactions may be excitatory and/or depressant and may include light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. Adverse effects of the

cardiovascular system are usually depressant and characterized by bradycardia, hypotension and cardiovascular collapse, which may lead to cardiac arrest.

The study has been designed to reduce these potential side effects as follows. The dosing regimen in this study is 0.5 mg/kg IV lidocaine administered as a slow push over 5 minutes. This dose was selected based on previous studies in human subject in which IV lidocaine has been administered to humans in ranges from 0.5 mg/kg to 2.2 mg/kg[1-5]. We selected a low dose to reduce the risk of side effects but still allow detection of drug serum concentrations for calculating PK parameters. In a heart with normal conduction and normal sinus rhythm, therapeutic levels of lidocaine cause little or no decrease in A-V conduction, and minimal cardiac slowing[1]. Lidocaine also has minimal hemodynamic effects in normal subjects, and causes minimal to no decrease in ventricular contractility, cardiac output, arterial pressure, or heart rate. Rapid IV bolus injections would lead to very high blood levels very quickly, which would be more likely to cause depressed cardiac function than a slowly administered IV injection given over 1 – 5 min[1]. For this reason, the IV injection in this study will be administered slowly over 5 minutes. Subjects will be connected to a SureSigns VM4 portable bedside monitor during the injection and for one hour after, for continuous noninvasive monitoring. This monitor has a 3-lead electrocardiogram (ECG) to monitor heart rate and rhythm, a pulse oximeter to monitor oxygen saturation (SpO_2,) and non-invasive blood pressure monitoring (NBP) capability. This is similar to monitoring that has been described previously in human subjects receiving IV lidocaine[4,6] and is also in agreement with the University of Iowa Hospitals and Clinics (UIHC) nursing committee protocol for monitoring with lidocaine injections. These parameters will be measured again prior to the subject leaving at the end of the procedure day. The Medically Accountable Investigator (MAI) (i.e., licensed clinician) will be in the hospital during all IV studies and will be available for consultation in the event that serious adverse events occur.

Additional risks include:

The standard risks of injection, including reactions which may occur because of the injection, excipients or administration include fever, local tenderness, abscess, tissue necrosis or infection at the site of injection, venous thrombosis or inflammation of the vein (phlebitis). These risks will be minimized by employing the expertise of the Clinical Research Unit (CRU) nursing staff for administering the IV injection. The injection site will be monitored for signs of infection during the study to minimize this risk. The standard risks of phlebotomy and venipuncture, including discomfort upon placement of an IV catheter, will consist of bruising at the site of blood draw, hypersensitivity to adhesive plasters or surgical tape, irritation at the catheter site, as well as a small risk of infection. These risks will be minimized by using sterile technique, as well as employing the expertise of the experienced nursing staff of the CRU. The catheter site will be monitored for signs of infection during the study to minimize this risk.

2.3.2. Known Potential Benefits

Participation in this study provides no direct benefit to the individual subjects. Society may benefit from the information obtained regarding the topical delivery of lidocaine, and how lidocaine patches compare to other topical reference products. This clinical protocol is part of an FDA U01 funded cooperative agreement, which is in response to the 5U01FD004275-03 “Critical Path Manufacturing Sector Research Initiative (U01).

3. OBJECTIVES

3.1. Study Objectives

The objectives of these studies are: 1) to determine the absolute bioavailability of lidocaine topical patches; 2) to determine the residual drug content in worn topical lidocaine patches; and 3) to apply mathematical models (e.g., deconvolution) to determine absorption rates from worn patches based on residual drug content and derived PK parameters.

3.2. Study Outcome Measures

The main outcome measure of the study is the determination of the pharmacokinetic parameters of lidocaine in healthy adult subjects; i.e., clearance (CL), volume of distribution (V), elimination rate constant (K_{el}), maximum serum concentration (C_{max}), time of maximum serum concentration (T_{max}) of lidocaine and area under the serum concentration-time curve (AUC). In addition, we will determine residual drug content from worn lidocaine patches to estimate total amount of absorbed lidocaine.

4. STUDY DESIGN

This is a three arm, open-label, crossover clinical pharmacokinetic (PK) study in 24 healthy human volunteers. The study will consist of 8 – 9 procedure days with a minimum 48 hour washout period between study arms. Two study arms are based on topical administration of lidocaine patches, and a third arm is based on IV administration. A study arm is defined as the entire administration and PK assessment period of either lidocaine topical patches or lidocaine hydrochloride injection.

The study products are:

- Lidoderm® patch 5% (Endo Pharmaceuticals)
- Lidocaine patch 5% (Mylan)
- Lidocaine hydrochloride 20 mg/1ml preservative free single dose vials

Each subject will be his/her own control and each subject will sign an Institutional Review Board (IRB) approved informed consent document explaining the purpose, nature, risks, benefits, and duration of the study. The study will be conducted in accordance with good clinical practice (GCP) guidelines and with the ethical principles originating in the Declaration of Helsinki.

The subject's skin in the area of application (skin of the lower back) will be relatively free of hair before patch application. Blood samples (approximately 5 mL each) will be drawn into vacutainer serum tubes. Blood samples will be obtained at the following time points (based on administration route):

- Within 60 minutes pre-patch application and then 1:00, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (patch removal), 14:00, 24:00, 27:00, 30:00, 33:00, 36:00, 39:00, 48:00 hours post-patch wear. Total of 18 samples for each patch used.
- Within 60 minutes pre-IV infusion and then 2, 5, 10, 20, 30, 45, 60 min, then 2:00, 3.00, 4:00, 6:00, 8:00, and 10:00 hours post injection. Total of 14 samples.

The total volume to be drawn from the subjects for the entire duration of the study will be approximately 250 mL or 17 tablespoons.

The half-life of topical lidocaine after patch removal is approximately 6 – 8 hours. Hence, 48 hours (i.e. ~5 to 6 half-lives) will be sufficient for >95% of lidocaine to be eliminated from the body after topical administration. The half-life after IV administration is approximately 1.5 – 2 hours. Ten hours of sampling will be sufficient for >95% of lidocaine to be eliminated from the body. Each subject will be enrolled to complete all study arms and procedure days. The study is open-label and not blinded because PK assessment is not subject to participant and/or observer bias. After each study arm is completed, the available safety data will be reviewed by an Independent Safety Monitor (ISM) to determine whether or not the subject will proceed to the next study arm.

A schedule of events is provided in **Appendix A**.

This study will be conducted in the CRU outpatient unit of the Institute for Clinical and Translational Science (ICTS) in the University of Iowa Hospitals and Clinics (UIHC). Conducting studies in this well-prepared research-oriented unit ensures that each subject is carefully observed throughout the study. If any adverse events occur, they can be properly documented and the subjects provided with the appropriate care. The CRU is a fully equipped research unit in UIHC, with inpatient and outpatient facilities, nursing staff on site and the MAI is available on- or offsite via the hospital pager system. The hospital code team is available to manage any unanticipated life-threatening emergency, and less urgent issues will be managed by the MAI.

5. STUDY ENROLLMENT AND WITHDRAWAL

Only adult subjects who meet the inclusion/exclusion criteria will be eligible for enrollment into this study. Twenty-four subjects will be recruited, with ten additional alternates who could replace subjects who drop out from the study for any reason. The study population selected for this study includes healthy adult men and women ages 18 to 65, inclusive. Enrollment will continue until 24 subjects complete the study. The selection criteria are designed to exclude persons who might have medical conditions that could pose a safety risk and persons whose medical conditions might interfere with the objectives and results of the study.

Subjects will be recruited by advertisements local to the study center. Potential subjects who are interested in the study will be informed of the study and if they wish to participate, will receive additional study information, including an informed consent document. Each of the 24 subjects enrolled will be expected to complete screening and all procedure days.

5.1. Subject Inclusion Criteria

Subjects are eligible for this study if they fulfill the inclusion criteria specified below:

1. Men or non-pregnant women, of any ethnic background, between the age of 18 and 65 years old.
2. Provide written informed consent before initiation of any study procedures.
3. Available for follow-up for the planned duration of the study.
4. Able to communicate well with the investigators.
5. Demonstrate comprehension of the protocol procedures and knowledge of study, as demonstrated by a study member filling out a consent checklist form to verify that the subject understands all aspects of the study including the purpose, procedures, risks and benefits.
6. Able to adhere to the study protocol schedule, study restrictions and examination schedule.
7. Subjects must be non-smokers and not regular users of tobacco. They must have refrained from regular and habitual use of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes) over the previous 12 months and must have not used any nicotine-containing products in the previous 30 days.
8. Subjects who are within their ideal body weight (BMI between 18-29.9 kg/m^2).
9. Subjects deemed to be healthy as judged by the Medically Accountable Investigator (MAI), as determined by medical history, physical examination, and medication history.
10. Negative urine drug screening test.
11. Have a normal blood pressure (systolic: 90-139 mmHg; diastolic: 60-89 mmHg) and heart rate (55-100 bpm).
12. Have normal screening laboratories for WBC, Hgb, Hct, platelets, sodium, potassium, chloride, bicarbonate, BUN, creatinine, ALT, AST.
13. Female subjects must be of non-childbearing potential. This is defined as surgically sterile (i.e. history of hysterectomy or tubal ligation), or postmenopausal for more than 1 year (no bleeding for 12 consecutive months). If the person is of childbearing potential they must be non-pregnant at the time of enrollment and on the morning of the first day of each study treatment procedure day (a urine pregnancy test will be administered if it has been >30 days since serum pregnancy test for enrollment). The person must also agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner.
14. Agrees not to participate in another clinical study during the study period unless the study is in the follow-up phase and it has been one month since the subject received any experimental agents

or treatments. The subject also agrees not to participate in an investigational drug study for at least 30 days after last procedure day.

15. Agrees not to donate blood to a blood bank throughout participation in the study and for at least 60 days after last procedure day.
16. Have a normal ECG; must not have any of the following: pathologic Q wave abnormalities, significant ST–T wave changes, left ventricular hypertrophy, right bundle branch block, left bundle branch block, advanced A-V heart block, non-sinus rhythm, excluding isolated premature atrial contractions (sinus rhythm is not between 55–100 beats per minute), or any other abnormality that, in the opinion of the MAI, makes it unsafe for the subject to participate in the study.

5.2. Subject Exclusion Criteria

Subjects will be excluded for any of the following conditions/reasons:

1. Women who are pregnant or lactating or have a positive serum pregnancy test at enrollment or positive urine pregnancy test at any time during the study.
2. Smokers. A "smoker", for the purposes of the study, will be defined as an individual who has regularly and habitually used nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes) over the past 12 months. Occasional recreational use (less than once monthly) will not warrant exclusion unless the individual has used nicotine-containing substances in the previous 30 days before study enrollment.
3. Participation in any ongoing investigational drug trial or clinical drug trial period unless the study is in the follow-up phase and it has been ≥ one month since the subject received any experimental agents or treatments.
4. Abnormal vital signs, defined as:
   - Hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) at rest on two separate days.
   - Heart rate <55 at rest on two separate days
   - Respiratory rate ≤ 11 to ≥ 18 breaths per minute
5. Temperature >38.0ºC (100.4ºF) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within seven days of administration of a study product.
6. History of chronic obstructive pulmonary disease.
7. Positive urine drug screening test.
8. Use of any prescription medication during the period 0 to 30 days or over-the counter medication during the period 0 to 3 days before entry to the study (vitamins, herbal supplements and birth control medications will be allowed).
9. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product. This includes antihistamines (within 72 hours prior to dosing), systemic or topical corticosteroids within four weeks prior to dosing, use of monoamine oxidase inhibitors 21 days prior to study, cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin [BCG], monoclonal antibodies, or radiation therapy.
10. Donation or loss of greater than one pint of blood within 60 days of entry to the study.
11. Any prior serious adverse reaction or hypersensitivity to lidocaine administered by any route.
12. Current diagnosis of any major psychiatric illness.
13. Received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within 30 days before enrollment in this study or expects to receive an experimental agent during the study.

14. Medical history of a serious chronic condition, including (but not limited to): allergic conditions such as anaphylaxis to food or drugs; asthma; generalized drug reactions; any seizure disorder; any central nervous system disorder; glaucoma (open or closed angle); history of pyloric or urinary bladder neck obstruction; intestinal obstruction; difficulty swallowing; stomach or bowel problems (e.g, blockage, muscle weakness, ulcerative colitis, Crohn's disease); bleeding disorders; acid reflux disease; myasthenia gravis; allergy to belladonna alkaloids; impaired hepatic or renal function.
15. Any condition that would, in the opinion of the Principal Investigator (PI) or MAI, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
16. Inability to communicate or cooperate with the investigators.
17. Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
18. History of significant dermatologic cancers (e.g. melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the investigative site.
19. History of consumption of alcohol within 24 hours prior to dose administration.
20. Subject has an obvious difference in skin color at patch sites (compared to neighboring skin), or the presence of a skin condition, excessive hair at the application site, sunburn, raised moles and scars, open sores at application site, scar tissue, tattoo, or coloration that would interfere with placement of test articles, or the assessment of the skin and/or reactions to drug.

5.3. Enrollment Procedures

5.3.1. Randomization Procedures

When found eligible to participate, the subject will be enrolled in one of the two study groups. The group assignment will be assigned based on alternating Group 1 or 2 for every other subject.

5.3.2. Masking Procedures

Not applicable.

5.3.3. Reasons for Withdrawal

The primary reason for a subject's discontinuation should be selected from the following standard categories:

Adverse Event **(AE) –** Clinical or laboratory events that in the judgment of the PI or MAI require discontinuation from the study in the best interest of subject. All AEs must have their relationship to the patch or IV injection assessed using the following terms: Associated or Not Associated. Upon occurrence of a Serious Adverse Event (SAE) possibly requiring discontinuation of a subject, the PI will confer with the ISM. If a subject is discontinued due to an AE, the event will be followed until it is adequately resolved.

Death

Protocol Deviation **–** The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements. The violation necessitated premature termination from the study as determined by the PI or MAI in consultation with the ISM.

Withdrawal of Consent **–** Subject desires to withdraw from further participation in the study in the absence of a medical need to withdraw as determined by the MAI. Subjects are free to withdraw from participating in the study at any time upon request.

Pregnancy

Other **–** Causes of premature termination from the study other than the above, such as suspension or termination of study, study site, or at investigator or Sponsor discretion.

5.3.4. Screen Failures

Subjects who signed an informed consent form and have undergone screening procedures, but who do not meet all entry criteria, will be considered screen failures and will not be enrolled. The reasons for screen failure will be documented. A screen failure also includes a screened subject who meets eligibility criteria but decides not to participate in the study.

5.3.5. Termination of Study

In the event that the study is discontinued, subjects will not progress on to the next procedure day. Enrolled subjects who have completed any procedure day will be followed for resolution of any ongoing AEs and will be contacted to evaluate the occurrence of any new AEs within 48 hours of the last procedure day completed.

5.3.6. Subject Discontinuations

The term "discontinuation" refers to a subject's non-completion of a study whether by their own choice, the PI/MAI/ISM's decision, or due to discontinuation of the study by the Sponsor. Subjects who discontinue prematurely after administration of the patch or IV injection will be replaced and their PK samples will be analyzed. Alternates will be recruited in the event study subjects are unavailable at the time of check in at the outpatient unit (CRU) or at any of the procedure days. It is expected that at least ten alternates will be recruited. An adequate number of alternates will be screened to ensure any dropouts can be replaced until a total of 24 subjects complete all study procedures.

5.3.7. Handling of Withdrawals

When handling withdrawals, every effort will be made to undertake protocol-specified safety follow-up procedures. However, should the subject decide to withdraw, the primary reason for withdrawal shall be recorded by a study team member in the subject's data collection form. Written withdrawal will be requested if the subject decides to withdraw by his or her own choice. The study team will attempt to collect safety data on any subject who leaves the study. If voluntary withdrawal occurs due to an AE, the subject will be asked to continue scheduled evaluations and be given appropriate care under medical supervision until the symptoms of any AE resolve or for 48 hours after completion of any study arm. Subjects who fail to return for the second or third procedure day or arm of the crossover study will be contacted by the site in an attempt to have them comply with the protocol. At a minimum, two phone calls and a certified, return receipt letter should be employed in an attempt to contact every subject who discontinues prematurely due to an AE.

6. STUDY PRODUCT

6.1. Study Product Description

6.1.1. Lidoderm® Patch 5%

Lidoderm® patch 5% is a prescription product that delivers approximately 3 ± 2% of the applied dose over a 12 hour wear time. At least 95% (665 mg) of lidocaine is expected to remain in the worn patch after removal.

6.1.2. Lidocaine HCl Injection, 20 mg/1 ml Preservative Free Single Dose Vials

Lidocaine hydrochloride injection is a prescription product that can be used for a variety of indications, including local anesthesia and treatment of ventricular arrhythmias.

6.1.3. Lidocaine Patch 5% (Mylan)

The Mylan lidocaine patch 5% is a prescription product that delivers approximately 11 ± 4% of the applied dose over a 12 hour wear time. At least 82% (115 mg) of lidocaine is expected to remain in the worn patch after removal.

6.2. Acquisition

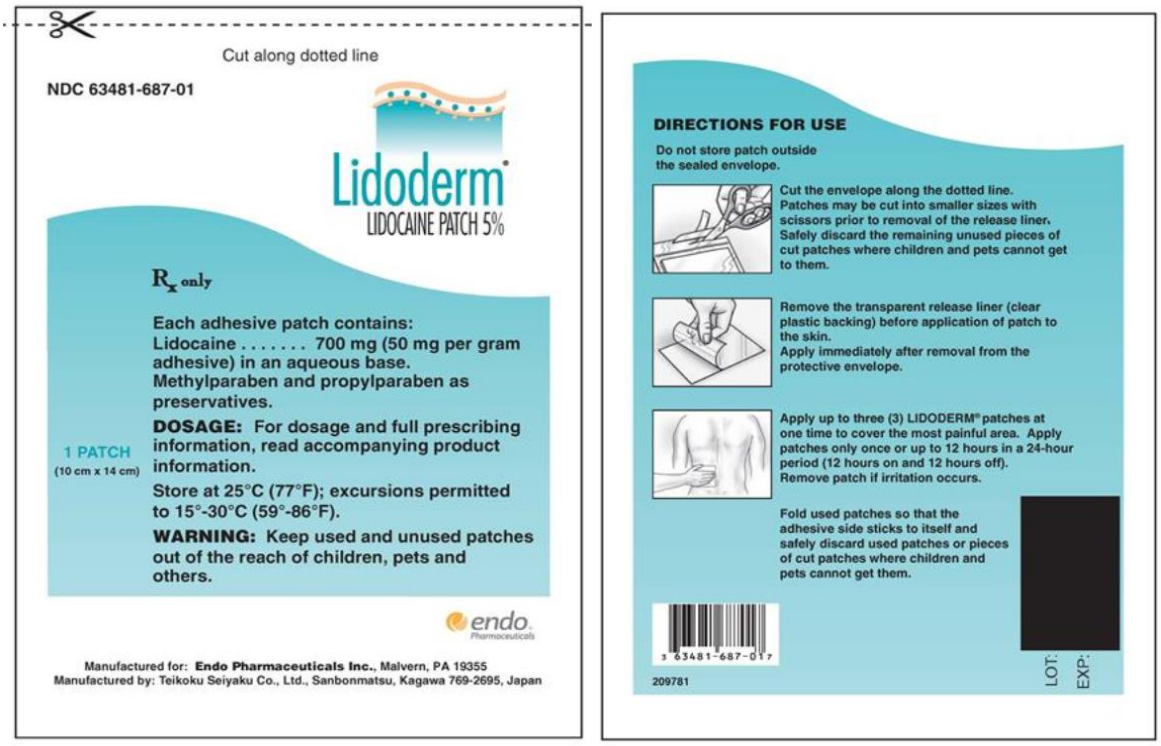
All drug products will be acquired through direct purchase by the Investigational Drug Services (IDS) pharmacy at UIHC.

Department of Pharmaceutical Care
Investigational Drug Services
University of Iowa Hospitals and Clinics
01284 PFP
200 Hawkins Drive
Iowa City, IA 52242
319-356-2577

6.3. Formulation, Packaging, and Labeling

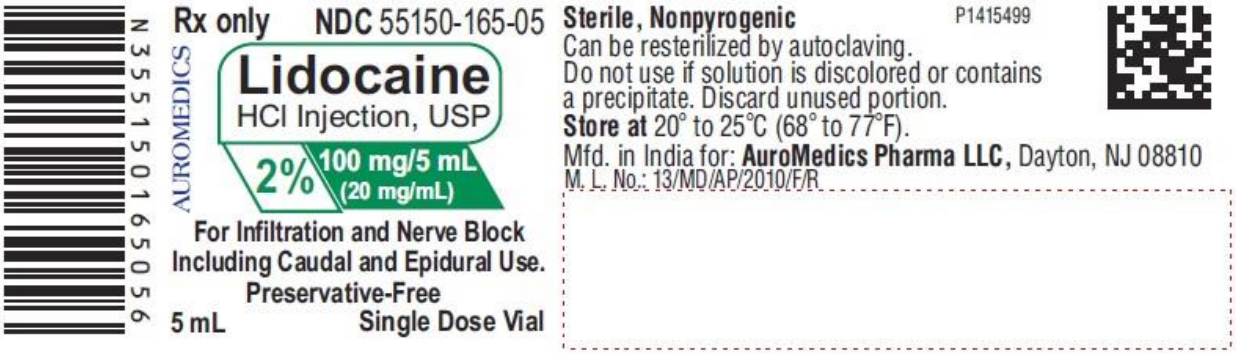
6.3.1. Lidoderm® Patch 5%

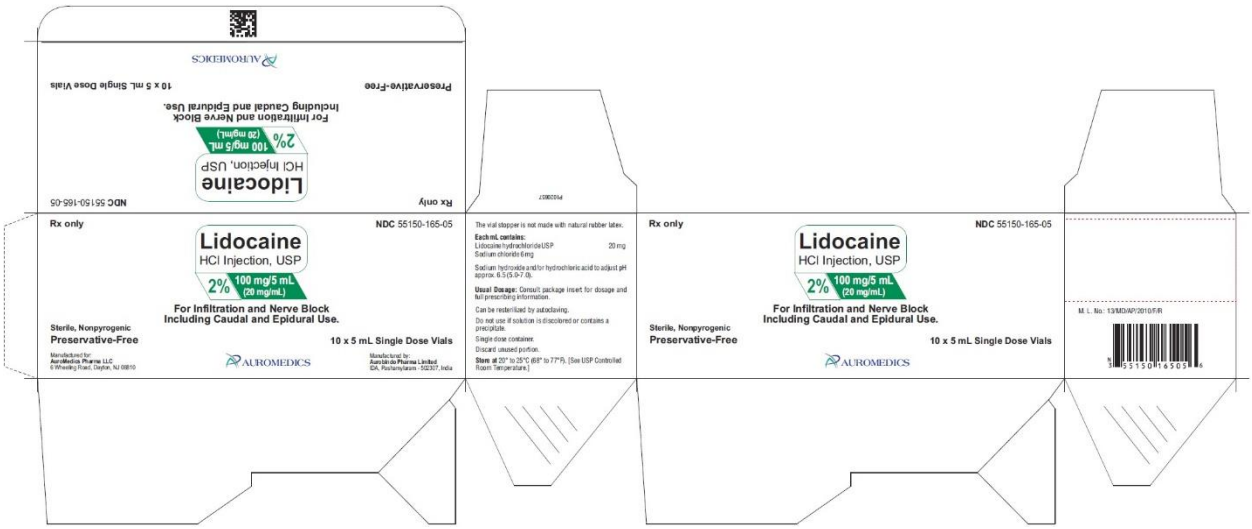
Active ingredient: lidocaine, 700 mg (50 mg per gram of adhesive). In addition to the active ingredient (lidocaine), the following inactive ingredients are present in the patch: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, and urea. This is a hydrogel patch manufactured by Endo Pharmaceuticals.



6.3.2. Lidocaine HCl Injection, 20 mg/1 ml Preservative Free Single Dose Vials

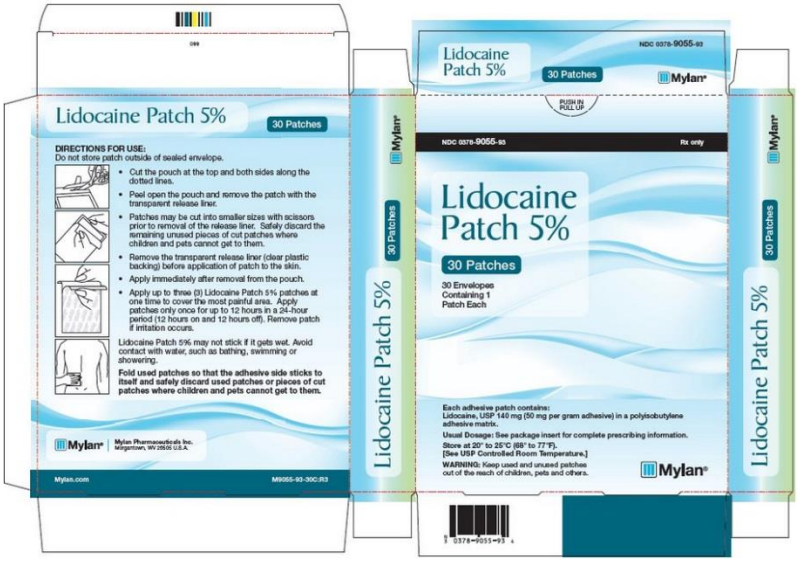
Active ingredient: lidocaine hydrochloride. Inactive ingredients: sodium chloride, sodium hydroxide, hydrochloric acid, and water. This injectable is manufactured by Auromedics Pharma LLC.





6.3.3. Lidocaine Patch 5% (Mylan)

Active ingredient: lidocaine, 140 mg (50 mg per gram of adhesive). The patch contains a polyisobutylene adhesive matrix. This is a matrix type patch manufactured by Mylan Pharmaceuticals.



6.4. Product Stability

Lidoderm® should be should be stored between 15-30°C (59-86 °F). The Mylan lidocaine 5% patch should be stored between 20-25°C (68-77°F). Lidocaine HCl injection should be stored at 15°-30°C (59°-86°F).

6.5. Dosage, Preparation and Administration of Study Product

6.5.1. Application of the Patch

The application site will be the skin of the mid to lower back. The subject's skin in the area of patch application will be healthy, clean, dry and relatively free of hair before patch application. Hair may be clipped (but not shaved) at the application site prior to patch application dosing, if necessary. A study team member will cleanse the site with water and carefully dry the skin prior to patch application. The patches will be applied to the skin and held firmly in place for 15 – 20 seconds after application. During the 12 hour patch wear time, the subjects will be asked to sit/lay quietly for the majority of their time, so as not to affect patch adhesion.

6.5.2. Administration of the IV Injection of Lidocaine Hydrochloride

A catheter will be inserted into the subject's arm, contralateral to the arm of the IV catheter that will be used for blood sampling. The site of the insertion for the catheter to administer lidocaine hydrochloride will be either near the elbow or the wrist depending on the identification of the vein in the subject. The IV will be injected over 5 minutes using an Alaris Guardrails pump with syringe pump cassette.

6.6. Accountability Procedures for the Study Product(s)

All drug products will be acquired through the University of Iowa IDS pharmacy. The products will be stored in the IDS pharmacy at the conditions noted in the package inserts. The IDS pharmacy will dispense the drug product to a study team member on the morning of, or the business day immediately before, a subject starts a new study arm. If the product is dispensed on the business day before a study, then it will be stored in a locked cabinet in the locked medication room in the CRU. Authorized badge access is required to access the medication room.

Department of Pharmaceutical Care
Investigational Drug Services
University of Iowa Hospitals and Clinics
01284 PFP
200 Hawkins Drive
Iowa City, IA 52242
Phone: 319-356-2577

Prior to dispensing the patch, the lot number on both the patch pouch and the product box will be recorded. Prior to dispensing the IV injection, the lot number of the product will be recorded. After removal, the used patches will be stored in sealable foil pouches labeled with subject ID number and shipped to Long Island University.

Ken Morris
Lachman Institute for Pharmaceutical Analysis
Long Island University – Brooklyn Campus
75 DeKalb Avenue, Room WL 313B
Brooklyn, New York 11201

6.7. Assessment of Subject Compliance with Study Product

Subjects will be directly observed at the time of patch application or IV administration by a member of the clinical research team. Administration will be documented on the clinical notes.

6.8. Patch System Adhesion Evaluation

Patch adhesion (for each patch being worn) will be evaluated and scored by study site personnel. The recommended scoring system for adhesion of patches will be adopted as described in the FDA draft Guidance included in **Appendix D**.

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4 = 0% adhered - patch detached (patch completely off the skin)

6.9. Concomitant Medications/Treatments

Any concomitant medication deemed necessary for the welfare of the subject during any arm of the study may be given at the discretion of the MAI. It is the responsibility of the PI to ensure that details regarding the medication are recorded in full in the subject's data collection forms, along with the routine documentation of any changes in concomitant medication that may have occurred during the study. Within four weeks prior to enrollment, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product or agents deemed to be immunosuppressive as determined by physician investigator is prohibited.

7. STUDY SCHEDULE

Study schedule is summarized in **Appendix A.**

7.1. Screening 0 to 30 Days

This study will be advertised through the UI campus-wide email system and through the University of Iowa Health Care "Noon News", a daily announcement flier printed for community and faculty members within UIHC. Individuals who call the study site will be provided with a brief overview of the purpose and study procedures. Prospective participants may be pre-screened through a telephone survey, if applicable. A copy of the informed consent document will be emailed to the prospective subject for them to review on their own time. If a subject is interested in study participation and passes pre-screening procedures, they will be invited to sign the informed consent document with a study team member (where they will again be provided overview of the study rationale, procedures, risks, and benefits). The individual must make the initiative to call the study center and schedule a meeting to sign the informed consent document. If the prospective participant cannot receive an informed consent document by email, the individual will be invited to review the document with a study team member, but must schedule a separate meeting to sign the document. This ensures that the individual has the chance to review the material in the informed consent on their own time.

It is recognized that the consent process must be carried out in an environment where no coercion is applied and where subjects can be adequately informed of the purpose, nature, procedures, risks and hazards of the study. One of the important features of our screening process is the ability for the prospective participant to leave the study site for review of the informed consent on his/her own time. This additionally demonstrates the reliability of the subject if they schedule a follow-up meeting to sign the informed consent. To assess and document comprehension of the material presented, the study member obtaining consent will complete a consent checklist to verify that the subject understands all aspects of the study including the purpose, procedures, risks and benefits. Checklists are signed by a member of the research team and made part of the permanent record. Prospective subjects will be carefully screened to ensure that they are in excellent physical and mental health. All women of childbearing potential will have a serum pregnancy test performed during screening.

After signing of the informed consent document a screening visit will be scheduled. It is possible for the screening visit to take place on the same day as the informed consent visit if scheduling allows. Screening evaluations will include:

- Questions about demographic information, medical history, and medication history
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate
- Height and weight
- ECG
- A brief physical exam, performed by the MAI or his designee
- Primary Skin Irritation (PSI) assessment for the site of patch application, completed by a study team member
- Urine drug of abuse screen
- Approximately 40 mL of blood will be collected from an arm or hand vein to test for the following:
  - Hematology parameters including Hgb, Hct, WBC and platelets
  - Chemistry parameters including sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT
  - Serum pregnancy test (if female of childbearing potential)

Subjects will satisfy all inclusion/exclusion requirements. All screening results will be evaluated against the inclusion/exclusion criteria to confirm subject eligibility (as defined in **section 5.1 and 5.2**). Laboratory results must be within the acceptable ranges in **Appendix B**; abnormal values may be repeated if believed to be a transient and non-clinically significant value. Any clinically significant abnormal laboratory will be shared with the subject and the subject will be advised to follow-up with their physician.

Subjects will be compensated for their time which is calculated as follows:

Screening visit:	$50
Procedure Day 1:	$175
Procedure Day 2:	$75
Procedure Day 3:	$25
Procedure Day 4:	$175
Procedure Day 5:	$175
Procedure Day 6:	$100
Procedure Day 7:	$25
Bonus completion of all visits:	$100
Total compensation:	$900.00

The money will be mailed directly from Accounts Payable to the subject in the form of a check for a total of $900.00. This payment schedule is based on the volunteer completing all study procedures. Failure to meet study requirements will result in a prorated payment determined by subject completion. This payment schedule will be followed for subjects in both groups.

7.2. Enrollment/Baseline

Total Planned Enrollment: 24 subjects and at least 10 alternates; however, enough alternates will be recruited to ensure 24 subjects complete screening and all seven procedure days. After eligible subjects are enrolled; they will be contacted to return to the CRU on the first procedure day. A washout period of a minimum of 48 hours after conclusion of each study arm will be ensured. Meals and snacks will be provided to the subjects during their stay at the CRU for the first day of each study arm.

7.2.1. Prohibitions and Restrictions

Potential subjects must be willing to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation.

1. Must have a negative urine pregnancy test on Day 1 of each study arm (pregnancy test will be administered only if it has been >30 days since the serum pregnancy test obtained as part of the screening procedures).
2. It is not recommended to consume food or beverages containing alcohol or caffeine for 24 hours prior to each PK sample collection day and until after the last PK sample is collected in each study arm.
3. Subjects should not be under the influence of alcohol, opiates, cocaine, amphetamines, benzodiazepines, hallucinogens, cannabinoids or barbiturates throughout the study. A positive urine drug test will exclude a subject from participating in the study.

4. If a subject has had a recent febrile illness within seven days of scheduled dosing, the start of study drug intake should be postponed until the body temperature is normal for at least 72 hours.
5. Subjects will be advised not to donate blood to a blood bank throughout participation in the study and for at least 60 days after the last procedure day or to participate in an investigational drug study for at least 30 days after completion of the study.
6. Must refrain from sunbathing and tanning for 48 hours prior to beginning of study and throughout the duration of the procedure days.

7.3. Study Visits and Procedures

Pivotal study (n = 24 subjects)
Since this is a crossover study, subjects will be divided into two groups (n = 12/group). The only difference between groups is the order in which they go through the study arms. There will be a minimum 48 hour washout period between study arms.

Group 1	**Group 2**
Study arm 1: Lidocaine 5% patches (Mylan) Study arm 2: Lidocaine injection Study arm 3: Lidoderm® 5% patches	Study arm 1: Lidoderm® 5% patches Study arm 2: Lidocaine injection Study arm 3: Lidocaine 5% patches (Mylan)

Group 1 study schedule

7.3.1. Procedure Day 1: Lidocaine Patch 5% (Mylan)

- Study staff will review any changes in medical history, medication history, and other study qualifications. All inclusion/exclusion criteria must continue to be met.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed within the 60 minutes prior to the application of the three patches.
- Urine pregnancy test will be obtained from women of childbearing potential if it has been more than 30 days since their last pregnancy test; the test must be negative.
- PSI assessment (as explained in **section 9.2.3.**) will be performed prior to patch application.
- The IV catheter will be placed under aseptic technique by an experienced nurse in the CRU.
- Approximately 5 mL of blood will be drawn within the 60 minutes prior to patch application.
- Time 0: Three lidocaine 5% patches (Mylan) will be applied by a member of the study team to the subject's lower back.
    - Each pouch will be numbered with a marker, and the patch corresponding to that pouch and release liner will be numbered the same. The pouches and release liners will be retained.
- Approximately 5 mL of blood will be drawn by an experienced nurse in the CRU at the following time points after patch application:
    - 1:00 hours ± 5 minutes after patch application (vital signs obtained)
    - 2:00 hours ± 5 minutes after patch application
    - 3:00 hours ± 5 minutes after patch application
    - 4:00 hours ± 5 minutes after patch application (vital signs obtained)
    - 5:00 hours ± 5 minutes after patch application
    - 6:00 hours ± 5 minutes after patch application

  - 8:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 10:00 hours ± 5 minutes after patch application
  - 12:00 hours ± 5 minutes after patch application (vital signs obtained, patches removed, and PSI recorded)
  - 14:00 hours ± 5 minutes after patch application (vital signs obtained)
- Adhesion assessment (as explained in **Appendix B**) will be performed at all time points while the subject is wearing the patches.
- If a patch has an adhesion score ≥2 at any time, a member of the study team may apply a small piece of medical tape to the corners of the patch in order to keep the patch in contact with the skin. Great care will be taken that the smallest area possible on the patch is covered by tape, so as not to alter drug absorption in any way.
- The patches will be removed at 12 hours. A PSI assessment will be recorded for each patch site.
- Upon removal, each patch will be placed back on its release liner (care will be taken to put the patch on the correct side of the release liner) and inserted into its original pouch. All three pouches will be placed together into a sealable foil pouch. Subject ID and date will be labeled on the outside of the foil pouch.
- The area of the skin where the patches were applied will be wiped with alcohol swabs (a different swab for each different patch site); the swabs will be numbered and placed into a second sealable foil pouch with the Subject ID and date.
- The day after removal, the patches will be shipped to Long Island University to be analyzed for residual drug content.
- Subjects are free to leave the facility but must arrive at the facility in time for scheduled blood draws the following day.

7.3.2. Procedure Day 2: Lidocaine Patch 5% (Mylan)

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed at the 24 and 39 hour time points.
  - Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:
    - 24:00 hours ± 30 minutes after patch application (vital signs obtained)
    - 27:00 hours ± 30 minutes after patch application
    - 30:00 hours ± 30 minutes after patch application
    - 33:00 hours ± 30 minutes after patch application
    - 36:00 hours ± 30 minutes after patch application
    - 39:00 hours ± 30 minutes after patch application (vital signs obtained)

Subjects are free to leave the facility between these visits and at the end of the day, but must arrive at the facility in time for scheduled blood draw the following day.

7.3.3. Procedure Day 3: Lidocaine Patch 5% (Mylan)

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed.
- Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:

  - 48:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility as this completes Arm 1 of the study.
- A total of 18 blood draws will be completed over a period of 48 hours (total blood volume drawn = approximately 90 mL).

7.3.4. Procedure Day 4: Lidocaine HCl Injection, 20 mg/1 ml Preservative Free Single Dose Vials

- Subject will return to the CRU after a minimum washout period of 48 hours from the last blood draw from Arm 1 of the study.
- Study staff will review any changes in medical history, medication history, and other study qualifications. All inclusion/exclusion criteria must continue to be met.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed within the 60 minutes prior to injection of lidocaine HCl.
- Urine pregnancy test will be obtained from women of childbearing potential if it has been more than 30 days since their last pregnancy test; the test must be negative.
- The IV catheter will be placed under aseptic technique by an experienced nurse in the CRU.
  - Approximately 5 mL of blood will be drawn within the 60 minutes prior to the injection of lidocaine HCl.
- The SureSigns VM4 monitor will be setup and attached to the subject for continuous monitoring of ECG, SpO_2, and blood pressure. Monitoring will start 5 minutes before administration of the IV lidocaine and will continue during and for one hour after the injection.
- Time 0: Using aseptic technique, an experienced nurse in the CRU will place an intravenous catheter in the opposite arm from the IV catheter used for blood sampling; this second catheter will be used for the IV lidocaine injection. Lidocaine HCl injection, 20 mg/1 ml preservative free single dose vials, dose 0.5 mg/kg, will be intravenously administered over 5 minutes using an Alaris Guardrails pump with syringe pump cassette. The catheter will be removed immediately upon completion of the injection.
- Blood sample collection will begin after the full injection has been administered. Approximately 5 mL of blood will be drawn by an experienced nurse in the CRU at the following time points after injection of the lidocaine HCl:
  - 2 minutes after the lidocaine HCl injection
  - 5 minutes after the lidocaine HCl injection
  - 10 minutes after the lidocaine HCl injection
  - 20 minutes after the lidocaine HCl injection
  - 30 ± 5 minutes after the lidocaine HCl injection
  - 45 ± 5 minutes after the lidocaine HCl injection
  - 1:00 hour ± 5 minutes after the lidocaine HCl injection (SureSigns VM4 monitor removed)
  - 2:00 hours ± 5 minutes after the lidocaine HCl injection (vital signs obtained)
  - 3:00 hours ± 5 minutes after the lidocaine HCl injection
  - 4:00 hours ± 5 minutes after the lidocaine HCl injection (vital signs obtained.
  - 6:00 hours ± 5 minutes after the lidocaine HCl injection
  - 8:00 hours ± 5 minutes after the lidocaine HCl injection (vital signs obtained)
  - 10:00 hours ± 5 minutes after the lidocaine HCl injection (SureSigns VM4 monitor used to monitor ECG, SpO_2, and blood pressure for 5 minutes)
- Subjects are free to leave the facility as this completes Arm 2 of the study.

- A total of 14 blood draws will be completed over a period of 10 hours (total blood volume drawn = approximately 70 mL).

7.3.5. Procedure Day 5: Lidoderm® Patch 5%

- Subject will return to the CRU after a minimum washout period of 48 hours from the last blood draw from Arm 2 of the study.
- Study staff will review any changes in medical history, medication history, and other study qualifications. All inclusion/exclusion criteria must continue to be met.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed within the 60 minutes prior to the application of the three patches.
- Urine pregnancy test will be obtained from women of childbearing potential if it has been more than 30 days since their last pregnancy test; the test must be negative.
- PSI assessment (as explained in **section 9.2.3.**) will be performed prior to patch application.
- The IV catheter will be placed under aseptic technique by an experienced nurse in the CRU.
- Approximately 5 mL of blood will be drawn within the 60 minutes prior to patch application.
- Time 0: Three Lidoderm® patches will be applied by a member of the study team to the subject's lower back.
  - Each pouch will be numbered with a marker, and the patch corresponding to that pouch and release liner will be numbered the same. The pouches and release liners will be retained.
- Approximately 5 mL of blood will be drawn by an experienced nurse in the CRU at the following time points after patch application:
  - 1:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 2:00 hours ± 5 minutes after patch application
  - 3:00 hours ± 5 minutes after patch application
  - 4:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 5:00 hours ± 5 minutes after patch application
  - 6:00 hours ± 5 minutes after patch application
  - 8:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 10:00 hours ± 5 minutes after patch application
  - 12:00 hours ± 5 minutes after patch application (vital signs obtained, patches removed, and PSI recorded)
  - 14:00 hours ± 5 minutes after patch application (vital signs obtained)
- Adhesion assessment (as explained in section **Appendix B**) will be performed at all time points while the subject is wearing the patches.
- If a patch has an adhesion score ≥2 at any time, a member of the study team may apply a small piece of medical tape to the corners of the patch in order to keep the patch in contact with the skin. Great care will be taken that the smallest area possible on the patch is covered by tape, so as not to alter drug absorption in any way.
- The patches will be removed at 12 hours. A PSI assessment will be recorded for each patch site.
- Upon removal, each patch will be placed back on its release liner (care will be taken to put the patch on the correct side of the release liner) and inserted into its original pouch. All three pouches will be placed together into a sealable foil pouch. Subject ID and date will be labeled on the outside of the foil pouch.
- The area of the skin where the patches were applied will be wiped with alcohol swabs (a different swab for each different patch site); the swabs will be numbered and placed into a second sealable foil pouch with the Subject ID and date.

- The day after removal, the patches will be shipped to Long Island University to be analyzed for residual drug content.
- Subjects are free to leave the facility but must arrive at the facility in time for scheduled blood draws the following day.

7.3.6. Procedure Day 6: Lidoderm® Patch 5%

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed at the 24 and 39 hour time points.
    - Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:
        - 24:00 hours ± 30 minutes after patch application (vital signs obtained)
        - 27:00 hours ± 30 minutes after patch application
        - 30:00 hours ± 30 minutes after patch application
        - 33:00 hours ± 30 minutes after patch application
        - 36:00 hours ± 30 minutes after patch application
        - 39:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility between these visits and at the end of the day, but must arrive at the facility in time for scheduled blood draw the following day.

7.3.7. Procedure Day 7: Lidoderm® Patch 5%

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed.
- Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:
    - 48:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility as this completes the study.
- A total of 18 blood draws will be completed over a period of 48 hours (total blood volume drawn = approximately 90 mL).

Group 2 study schedule

7.3.8. Procedure Day 1: Lidoderm® Patch 5%

- Study staff will review any changes in medical history, medication history, and other study qualifications. All inclusion/exclusion criteria must continue to be met.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed within the 60 minutes prior to the application of the three patches.
- Urine pregnancy test will be obtained from women of childbearing potential if it has been more than 30 days since their last pregnancy test; the test must be negative.
- PSI assessment (as explained in **section 9.2.3**.) will be performed prior to patch application.
- The IV catheter will be placed under aseptic technique by an experienced nurse in the CRU.
- Approximately 5 mL of blood will be drawn within the 60 minutes prior to patch application.
- Time 0: Three Lidoderm® patches will be applied by a member of the study team to the subject's lower back.

    - Each pouch will be numbered with a marker, and the patch corresponding to that pouch and release liner will be numbered the same. The pouches and release liners will be retained.
- Approximately 5 mL of blood will be drawn by an experienced nurse in the CRU at the following time points after patch application:
    - 1:00 hours ± 5 minutes after patch application (vital signs obtained)
    - 2:00 hours ± 5 minutes after patch application
    - 3:00 hours ± 5 minutes after patch application
    - 4:00 hours ± 5 minutes after patch application (vital signs obtained)
    - 5:00 hours ± 5 minutes after patch application
    - 6:00 hours ± 5 minutes after patch application
    - 8:00 hours ± 5 minutes after patch application (vital signs obtained)
    - 10:00 hours ± 5 minutes after patch application
    - 12:00 hours ± 5 minutes after patch application (vital signs obtained, patches removed, and PSI recorded)
    - 14:00 hours ± 5 minutes after patch application (vital signs obtained)
- Adhesion assessment (as explained in **Appendix B**) will be performed at all time points while the subject is wearing the patches.
- If a patch has an adhesion score ≥2 at any time, a member of the study team may apply a small piece of medical tape to the corners of the patch in order to keep the patch in contact with the skin. Great care will be taken that the smallest area possible on the patch is covered by tape, so as not to alter drug absorption in any way.
- The patches will be removed at 12 hours. A PSI assessment will be recorded for each patch site.
- Upon removal, each patch will be placed back on its release liner (care will be taken to put the patch on the correct side of the release liner) and inserted into its original pouch. All three pouches will be placed together into a sealable foil pouch. Subject ID and date will be labeled on the outside of the foil pouch.
- The area of the skin where the patches were applied will be wiped with alcohol swabs (a different swab for each different patch site); the swabs will be numbered and placed into a second sealable foil pouch with the Subject ID and date.
- The day after removal, the patches will be shipped to Long Island University to be analyzed for residual drug content.
- Subjects are free to leave the facility but must arrive at the facility in time for scheduled blood draws the following day.

7.3.9. Procedure Day 2: Lidoderm® Patch 5%

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed at the 24 and 39 hour time points.
    - Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:
        - 24:00 hours ± 30 minutes after patch application (vital signs obtained)
        - 27:00 hours ± 30 minutes after patch application
        - 30:00 hours ± 30 minutes after patch application
        - 33:00 hours ± 30 minutes after patch application
        - 36:00 hours ± 30 minutes after patch application

    - 39:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility between these visits and at the end of the day, but must arrive at the facility in time for scheduled blood draw the following day.

7.3.10. Procedure Day 3: Lidoderm® Patch 5%

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed
- PSI assessment (as explained in **section 9.2.3.**) will be performed.
- Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist at the CRU at:
    - 48:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility as this completes Arm 1 of study.
- A total of 18 blood draws will be completed over a period of 48 hours (total blood volume drawn = approximately 90 mL).

7.3.11. Procedure Day 4: Lidocaine HCl Injection, 20 mg/1 ml Preservative Free Single Dose Vials

- Subject will return to the CRU after a minimum washout period of 48 hours from the last blood draw from Arm 1 of the study.
- Study staff will review any changes in medical history, medication history, and other study qualifications. All inclusion/exclusion criteria must continue to be met.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed within the 60 minutes prior to injection of lidocaine HCl.
- Urine pregnancy test will be obtained from women of childbearing potential if it has been more than 30 days since their last pregnancy test; the test must be negative.
- The IV catheter will be placed under aseptic technique by an experienced nurse in the CRU.
    - Approximately 5 mL of blood will be drawn within the 60 minutes prior to the injection of lidocaine HCl.
- The SureSigns VM4 monitor will be setup and attached to the subject for continuous monitoring of ECG, SpO_2, and blood pressure. Monitoring will start 5 minutes before administration of the IV lidocaine and will continue during and for one hour after the injection.
- Time 0: Using aseptic technique, an experienced nurse in the CRU will place an intravenous catheter in the opposite arm from the IV catheter used for blood sampling; this second catheter will be used for the IV lidocaine injection. Lidocaine HCl injection, 20 mg/1 ml preservative free single dose vials, dose 0.5 mg/kg, will be intravenously administered over 5 minutes using an Alaris Guardrails pump with syringe pump cassette. The catheter will be removed immediately upon completion of the injection.
- Blood sample collection will begin after the full injection has been administered. Approximately 5 mL of blood will be drawn by an experienced nurse in the CRU at the following time points after injection of the lidocaine HCl:
    - 2 minutes after the lidocaine HCl injection
    - 5 minutes after the lidocaine HCl injection
    - 10 minutes after the lidocaine HCl injection
    - 20 minutes after the lidocaine HCl injection
    - 30 ± 5 minutes after the lidocaine HCl injection

- 45 ± 5 minutes after the lidocaine HCl injection
- 1:00 hour ± 5 minutes after the lidocaine HCl injection (SureSigns VM4 monitor removed)
- 2:00 hours ± 5 minutes after the lidocaine HCl injection (vital signs obtained)
- 3:00 hours ± 5 minutes after the lidocaine HCl injection
- 4:00 hours ± 5 minutes after the lidocaine HCl injection (vital signs obtained)
- 6:00 hours ± 5 minutes after the lidocaine HCl injection
- 8:00 hours ± 5 minutes after the lidocaine HCl injection (vital signs obtained)
- 10:00 hours ± 5 minutes after the lidocaine HCl injection (SureSigns VM4 monitor used to monitor ECG, SpO_2, and blood pressure for 5 minutes)

- Subjects are free to leave the facility as this completes Arm 2 of the study.
- A total of 14 blood draws will be completed over a period of 10 hours (total blood volume drawn = approximately 70 mL).

7.3.12. Procedure Day 5: Lidocaine Patch 5% (Mylan)

- Subject will return to the CRU after a minimum washout period of 48 hours from the last blood draw from Arm 2 of the study.
- Study staff will review any changes in medical history, medication history, and other study qualifications. All inclusion/exclusion criteria must continue to be met.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate will be performed within the 60 minutes prior to the application of the three patches.
- Urine pregnancy test will be obtained from women of childbearing potential if it has been more than 30 days since their last pregnancy test; the test must be negative.
- PSI assessment (as explained in **section 9.2.3**.) will be performed prior to patch application.
- The IV catheter will be placed under aseptic technique by an experienced nurse in the CRU.
- Approximately 5 mL of blood will be drawn within the 60 minutes prior to patch application.
- Time 0: Three lidocaine 5% patches (Mylan) will be applied by a member of the study team to the subject's lower back.
  - Each pouch will be numbered with a marker, and the patch corresponding to that pouch and release liner will be numbered the same. The pouches and release liners will be retained.
- Approximately 5 mL of blood will be drawn by an experienced nurse in the CRU at the following time points after patch application:
  - 1:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 2:00 hours ± 5 minutes after patch application
  - 3:00 hours ± 5 minutes after patch application
  - 4:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 5:00 hours ± 5 minutes after patch application
  - 6:00 hours ± 5 minutes after patch application
  - 8:00 hours ± 5 minutes after patch application (vital signs obtained)
  - 10:00 hours ± 5 minutes after patch application
  - 12:00 hours ± 5 minutes after patch application (vital signs obtained, patches removed, and PSI recorded)
  - 14:00 hours ± 5 minutes after patch application (vital signs obtained)
- Adhesion assessment (as explained in **Appendix B**) will be performed at all time points while the subject is wearing the patches.
- If a patch has an adhesion score ≥2 at any time, a member of the study team may apply a small piece of medical tape to the corners of the patch in order to keep the patch in contact

with the skin. Great care will be taken that the smallest area possible on the patch is covered by tape, so as not to alter drug absorption in any way.
- The patches will be removed at 12 hours. A PSI assessment will be recorded for each patch site.
- Upon removal, each patch will be placed back on its release liner (care will be taken to put the patch on the correct side of the release liner) and inserted into its original pouch. All three pouches will be placed together into a sealable foil pouch. Subject ID and date will be labeled on the outside of the foil pouch.
- The area of the skin where the patches were applied will be wiped with alcohol swabs (a different swab for each different patch site); the swabs will be numbered and placed into a second sealable foil pouch with the Subject ID and date.
- The day after removal, the patches will be shipped to Long Island University to be analyzed for residual drug content.
- Subjects are free to leave the facility but must arrive at the facility in time for scheduled blood draws the following day.

7.3.13. Procedure Day 6: Lidocaine Patch 5% (Mylan)

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed at the 24 and 39 hour time points.
    - Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:
        - 24:00 hours ± 30 minutes after patch application (vital signs obtained)
        - 27:00 hours ± 30 minutes after patch application
        - 30:00 hours ± 30 minutes after patch application
        - 33:00 hours ± 30 minutes after patch application
        - 36:00 hours ± 30 minutes after patch application
        - 39:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility between these visits and at the end of the day, but must arrive at the facility in time for scheduled blood draw the following day.

7.3.14. Procedure Day 7: Lidocaine Patch 5% (Mylan)

- A brief symptom-directed physical exam, if indicated.
- Vital signs to determine blood pressure, pulse, temperature, and respiratory rate.
- PSI assessment (as explained in **section 9.2.3.**) at patch application sites will be performed.
- Approximately 5 mL of blood will be drawn by an experienced nurse or phlebotomist in the CRU at:
    - 48:00 hours ± 30 minutes after patch application (vital signs obtained)
- Subjects are free to leave the facility as this completes the study.
- A total of 18 blood draws will be completed over a period of 48 hours (total blood volume drawn = approximately 90 mL).

7.4. Early Termination Visit

An Early Termination Visit should be performed for any subject who discontinues their participation in the study prior to completing all procedure days. If a subject leaves the study before the last

procedure day, the subject will be asked about his/her reasons for termination. This may occur via telephone call or by email from a member of the study team. If the subject identifies one or more adverse events as their reason, then a brief physical exam should be performed. All withdrawals will be documented on a subject withdrawal form for study records.

7.5. Unscheduled Visit

If an unscheduled visit occurs, a member of the study team will interview and evaluate the subject to determine the cause of the visit and provide care as needed and information documented on a supplemental visit form.

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

Serum pregnancy tests will be performed at the screening visit before enrollment for all women of childbearing potential. Urine pregnancy tests will be performed on the morning of the first day of each of the three study arms if it has been more than 30 days since the subject's negative serum pregnancy test. If any test is positive, the subject will be excluded from further participation, counseled, and referred to a clinical facility.

On each of the procedure days, the subjects will be interviewed about any new, continuing, or worsening symptoms. Vital signs will be recorded before patch application or IV injection and at specified times in each procedure day (as indicated in **section 7.3.**). A CRU nurse or member of the study team will determine if the subject has any reportable symptoms. If appropriate, the MAI will be contacted and a symptom-directed physical exam will be completed. Results of the physical examinations and vital sign assessments will be reported to the ISM to determine if there is evidence of immediate safety concerns or for changes in values that indicate a potential danger to the subject should the subject continue in the study. After conclusion of each study arm and discharge from the CRU, subjects will be asked to report all adverse events (AE) for up to 48 hours. Subjects will be interviewed by telephone daily for two consecutive days (up to 48 hours) after the last procedure day of each study arm to determine if any AE occurred in the 48 hours post-discharge. If an event is judged to be a Serious Adverse Event (SAE), an SAE data collection form will be completed and SAE reporting procedures followed.

8.2. Laboratory Evaluations

8.2.1. Clinical Laboratory Evaluations

In the event of an AE (of moderate severity or more) or SAE, safety laboratory data will be drawn, including hematology and chemistry parameters and provided to the MAI and ISM. Chemistry parameters include sodium, potassium, chloride, bicarbonate, BUN, creatinine, AST, ALT. Hematology parameters include Hgb, Hct, WBC and platelets. All tests are considered normal if the parameters are within normal limits or acceptable ranges, according to **Appendix B**.

8.2.2. Bioanalytical Methods

Serum samples will be analyzed using validated quantitation methods, which will be developed and performed by Ken Morris, PhD, and his laboratory members at Long Island University. Dr. Morris' group will meet conditions in the FDA guidance for Bioanalytical Method Validation 2012.

8.2.3. Method for Determining Drug Content in Worn and Unworn Transdermal Systems

8.2.3.1. Worn Systems

For the determination of residual content, the used patches will be sent to Ken Morris' laboratory at Long Island University on the day after the patches are removed from the subject using expedited, temperature-controlled, next day delivery service. The appropriate extraction technique will be determined and developed by Dr. Morris' group.

8.2.3.2. Unworn Systems

A minimum of 10 unworn systems from the same lot number worn by the subjects will be analyzed for drug content.

The amount of drug absorbed will be calculated as follows:
Amount of drug absorbed=mean amount of drug in unworn systems – amount of drug in worn system

8.3. Specimen Preparation Handling and Shipping

8.3.1. Instructions for Specimen Preparation, Handling, and Storage

Blood samples will be collected during the procedures days at the time points specified in **section 4**. The CRU has a small well-equipped laboratory on site with a trained laboratory technician available to process the samples as required for this study, and the study coordinator/study team members will be available to assist with sample processing. The PI also has a well-equipped laboratory with appropriate equipment for sample processing. After processing, all samples will be stored in Dr. Brogden's lab at -80°C until shipped to Long Island University. During sample processing, the sera will be separated into two aliquots. One set of aliquots will be analyzed using an LC-MS validated method at Long Island University while the other set will be stored separately at the UI College of Pharmacy as a back-up set of samples.

8.3.2. Specimen Shipment

Serum samples will be shipped to Long Island University for analysis using expedited temperature-controlled, next-day delivery service.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Assessment of AEs throughout each of the procedure days will be monitored and vital signs (blood pressure, temperature, pulse, and respiratory rate) for each subject will be periodically monitored. AEs at the patch application site (e.g., erythema, edema, itching) will be assessed subjectively by each subject and also examined by a member of the study team at study visits following patch removal. Subjects will be interviewed by telephone daily for two consecutive days (up to 48 hours) after completing each study arm to determine if any AEs occurred in the 48 hours following study arm completion. If any skin changes are noted by the subject, (s)he will be instructed to return to the CRU for evaluation. If any skin changes are seen on exam they will be defined as topical AEs. In addition, the MAI will be available to assess and treat (where indicated). When medically indicated, the subject will be admitted to UIHC for emergency and/or continued care. All adverse effects will be reviewed by the ISM, and all SAEs will be immediately reported to the IRB.

The administration of lidocaine is not anticipated to cause clinical problems. If a clinical problem would occur the subject will be discontinued from the study. If AEs occur, clinical judgment will be used with the results recorded as part of the PI or MAI's judgment of the probability that an event is linked to the procedure. Subjects will be followed until all AEs are resolved or until they become medically stable.

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1. Adverse Events

AEs are qualified by expectedness, grade of severity, relationship of causality, and as serious or non-serious based on the definitions provided (**Appendices B and C**). All events will be recorded on appropriate clinical report forms with notation of duration, severity, and outcome. The PI is responsible for recording all AEs that are observed or reported during the study, regardless of their relationship to investigational product or their clinical significance.

9.2.1.1. Adverse Event Definition

Any untoward medical occurrence in a subject administered a study product, which does not necessarily have a causal relationship with this procedure. An AE is defined as any noxious, pathologic, or unintended change in anatomic, physiologic, or metabolic functions, as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical study, regardless of their relationship to study product. The occurrence of an AE may come to the attention of study personnel during study visits or interviews of a subject presenting for medical care, or upon review by a study monitor. AEs include:

- An exacerbation of a pre-existing condition
- A concurrent illness
- Any drug interaction
- Any event related to a concomitant medication

An AE can be any unfavorable and unintended sign (including an abnormal finding), symptom or disease temporarily associated with the use of a study product, whether or not related to the study product. This includes any occurrence that is new in onset or aggravated

in severity or frequency from the baseline condition, abnormal results of diagnostic procedures (including laboratory test abnormalities) which are considered AEs if they:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, assessment of severity, relationship to study product (assessed only by the PI or MAI), and time of resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately regardless of relationship. All AEs will be followed until the subject becomes medically stable. Elective hospitalizations for pre-study conditions (e.g., elective cosmetic procedures) are not AEs.

9.2.2. Grading Scale for Severity of AEs

AEs are to be graded according to the standard criteria in **Appendix B and C**. The definitions provided in this section will be applied if there are no standard criteria given for that particular event.

- Mild: events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life Threatening: any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

9.2.3. Reactogenicity

Adverse events associated with topical administration will vary based on formulation and extent of systemic absorption. Dermatology reactions from the topical patch include blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. Other possible systemic reactions include bradycardia, apprehension, confusion, dizziness, drowsiness, paresthesia, nausea, vomiting, bruising, methemoglobinemia, weakness, and angioedema or anaphylactic hypersensitivity reactions. Also please refer to the attached package inserts.
The adverse events associated with systemic lidocaine administration may be cardiovascular, central nervous system, gastrointestinal, neuromuscular and skeletal, respiratory, or miscellaneous in nature. The majority of these reactions do not have a defined frequency of occurrence, and many will vary with route of administration and are dose-related. Cardiovascular

effects may include bradycardia, cardiac arrhythmia, circulatory shock, coronary artery vasospasm, edema, flushing, heart block, hypotension, or local thrombophlebitis. Central nervous system effects may include agitation, anxiety, apprehension, coma, confusion, disorientation, dizziness, drowsiness, euphoria, hallucination, hyperesthesia, hypoesthesia, intolerance to temperature, lethargy, loss of consciousness, metallic taste, nervousness, paresthesia, psychosis, seizure, slurred speech, and twitching. Respiratory reactions include bronchospasm, dyspnea, respiratory depression. Other/miscellaneous possible adverse events include nausea, vomiting, tremor, weakness, tinnitus, and anaphylaxis or hypersensitivity reactions. Asystole and methemoglobinemia have occurred in less than 1% of patients.

If an event has not been experienced previously and is not listed here, it will be categorized as an "Unexpected" AE.

Primary Skin Irritation (PSI) Assessment
PSI will be performed pre-dose, and at 12:00 hours (after patch removal), 24:00 hours, 39:00 and 48:00 hours. The skin site will be graded according to the following irritation grading scale:

0 - No evidence of irritation.
1 - Faint but definite erythema, no eruptions or broken skin or no erythema but definite dryness; may have epidermal fissuring.
2 - Moderate erythema, may have a few papules or deep fissures, moderate-to-severe erythema in the cracks.
3 - Severe erythema (beet redness), may have generalized papules or moderate-to-severe erythema with slight edema (edges well defined by raising).
4 - Generalized vesicles or eschar formations or moderate-to-severe erythema and/or edema extending beyond the area of the patches.

A CRU nurse or member of the study team will evaluate each subject for the occurrence of reactogenicity symptoms by assessing signs and reported symptoms by the subject and by reviewing the subject's vital signs. A physical examination by the MAI will be conducted when appropriate.

9.2.4. Serious Adverse Events

A SAE is defined as an AE that results in any of the following outcomes:

- Death
- Life-threatening event
- Inpatient hospitalization (>24 hrs) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life-threatening (any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that had it occurred in a more severe form, might have caused death), or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Additionally, the occurrence of the following reactogenicity symptoms is defined as an SAE:

- Any Grade 4 reactogenicity

9.3. Reporting Procedures

9.3.1. Serious Adverse Events

The PI must report to the FDA Sponsor and the Research Involving Human Subject Committee (RIHSC) any unanticipated problems involving risk to human subjects or others according to 21 CFR 312.32(c)(2). Anticipated adverse events may be reported to the RIHSC in the annual report for continuing review.

However, certain adverse events must be reported to the RIHSC within 7 working days of the discovery of the event. The RIHSC defines these adverse events as including, but not limited to the following:

- An adverse event that is not expected, i.e. not listed in the informed consent document or the investigator's brochure;
- An expected adverse event that occurs at a greater frequency or duration than expected;
- Any adverse event that would require modification of the protocol and/or informed consent document.

The following procedures will occur if in the opinion of the PI, MAI or ISM the event meets the criteria of a SAE:

- All SAEs will be:
  - reviewed by a study physician
  - recorded on the appropriate AE and SAE form
  - followed by the MAI until satisfactory resolution or until the MAI deems the event to be chronic or the subject to be stable

Any AE considered serious by the PI, MAI, or ISM or which meets the aforementioned criteria must be submitted on an SAE form to the FDA at the following address:

Caroline Strasinger, PhD
Branch Chief – Chemistry, Manufacturing and Controls at FDA
FDA / CDER / Office of Pharmaceutical Quality / Office of Lifecycle Drug Product
301-796-3776 (Office)
502-249-1839 (Cell)
caroline.strasinger@fda.hhs.gov

In addition, such events will be reported to the IRB in accordance with IRB policy. The PI will complete an SAE form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on an SAE Form and sent by email to the FDA within 24 hours of site awareness.
- SAEs other than death and immediately life-threatening events, regardless of relationship, will be reported via email by the site within 24 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by the FDA Pharmacovigilance Group and should be provided as soon as possible. All SAEs will be followed until satisfactory resolution or until the MAI deems the event to be chronic or the subject to be stable. The FDA Clinical Project Manager will be notified of the SAE by the FDA Pharmacovigilance Group. The FDA Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

9.3.2. Reporting of Pregnancy

Subjects must be of non-childbearing potential, or if of childbearing potential (as determined by the MAI or PI) must be practicing abstinence or using an effective licensed method of birth control (e.g., use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), condoms with spermicidal agents; or have a vasectomized partner). Female subjects will undergo serum pregnancy tests during the Screening Period. Pregnant or lactating women will be excluded from the study. If an eligible female subject has a positive urine pregnancy test on any of the procedure days, she will not be permitted to participate that day and will be discontinued from the study.

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

The administration of lidocaine is not anticipated to cause significant clinical problems. If a clinical problem would occur the subject will be discontinued from the study. If AEs occur, clinical judgment will be used with the results recorded as part of the PI or MAI judgment of the probability that an event is linked to the lidocaine procedure.

9.5. Halting Rules

The ISM will review reports on protocol progress, side effects and AEs after each study arm. The PI will be informed of all SAE reports within 24 hours of their occurrence. All SAEs will be reported by the PI to the MAI, ISM, the University of Iowa IRB, and the appropriate FDA program officer. The PI will provide an initial SAE report within 24 hours of their occurrence to the ISM, University of Iowa IRB, and FDA program officer, or as soon as required by each entity, with a final report to follow.

Dosing will be halted and the data reviewed by the ISM if any of the following are observed:

- 3 or more subjects develop Grade 2 or higher of the major side-effects known to be related to lidocaine
- 2 or more subjects develop Grade 3 or higher of the major side-effects known to be related to lidocaine
- Any single SAE

When the study is halted then the PI, MAI, and ISM will determine whether further procedure days or study arms should be stopped, and/or if protocol or informed consent is modified.

9.6. Safety Oversight

The ISM is a physician at the enrollment site with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion at each site. The primary focus of the ISM is to independently review all SAEs, thoroughly investigate those events considered unexpected, and provide an independent assessment to the FDA. Participation is for the duration of the study. The ISM will review available safety data provided for each subject after each study arm prior to making a recommendation to proceed to the next study arm. A “study arm” encompasses the administration of the product (patches or IV) and all associated procedure days. Ad hoc meetings with the FDA and MAI/PI may be required if a halting rule occurs. The ISM should be able to readily access all subject records in real time. This is accomplished by review of SAEs, immediately after they occur, with follow-up through resolution, or until the MAI/ISM deems the subject medically stable.

The ISM may be a faculty member at the clinical site, but will not be under the direct supervision of the PI. It is the responsibility of the PI to ensure that the ISM is appraised of all new safety information relevant to the study product and the study. This includes providing the ISM with all safety reports issued by the sponsor. The ISM should receive all protocol revisions and may receive other documents related to the study. The ISM will review all SAEs which occur during the course of the study. The ISM may transiently halt enrollment. The ISM will contact the MAI and PI, and the medical officer at the FDA for any event that needs further evaluation.

9.7. Clinical Monitoring

9.7.1. Site Monitoring Plan

Site monitoring is conducted to ensure that the human subject protection, study procedures, laboratory, study product administration and data collection processes are of high quality and meet sponsor, ICH E6, and other appropriate, regulatory guidelines and that the study is conducted in accordance with the protocol and sponsor standard operating procedures. Site visits may be conducted by an authorized representative of the FDA or other regulatory agencies to inspect study data, subjects' medical records and CRFs in accordance with ICH guidelines, Good Clinical Practice (GCP) and the respective local and national government regulations and guidelines. The investigator will permit authorized representatives of the FDA and the respective local and national health or regulatory authorities to inspect facilities and records relevant to this study if needed. The PI and MAI will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

FDA-designated clinical monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the FDA.

10. PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

10.1. Study Hypotheses

The main objective of this study is to determine the absolute bioavailability and PK parameters (e.g., AUC, C_{max}, T_{max}, CL, V) of lidocaine in healthy adults after using lidocaine 5% patches manufactured by Endo Pharmaceuticals and Mylan. The secondary objective is to determine residual drug content in worn patches.

10.2. Pharmacokinetic (PK) Analyses

Lidocaine concentrations will be measured in serum samples collected from each subject. Blood samples (approximately 5 mL each) will be collected at the time points list in **section 4**. Actual sampling times will be used to estimate PK parameters.

Non compartmental and compartmental analyses will be conducted to estimate the primary PK parameters such as clearance (CL), volume of distribution (V), elimination rate constant (K_{el}), maximum serum concentration (C_{max}), time of maximum serum concentration (T_{max}) and area under the serum concentration-time curve (AUC). Absolute bioavailability will be calculated as follows:

$$Absolute\ bioavilability = \frac{AUC_{patch}/Dose_{patch}}{AUC_{IV}/Dose_{IV}}$$

Equation 1: For determination of the absolute bioavailability for the Lidoderm® 5% patches (Endo Pharmaceuticals) and the lidocaine 5% patches (Mylan). The patch refers to the topical lidocaine patch systems. The geometric means for $AUC_{0-\infty}$ will be obtained by exponentiating the log transformed $AUC_{0-\infty}$ for the two treatments to determine the absolute bioavailability.

Different mathematical approaches including, but not limited to, deconvolution will then be utilized to determine secondary objectives and the rate of drug delivery from the patches. The secondary objective to determine residual drug content in worn patches would provide a surrogate method to determine the amount of drug delivered *in vivo* after wearing the patch. The following equation will be used to determine the amount of drug delivered *in vivo*:

$$Lidocaine\ released = Total\ lidocaine - residual\ lidocaine$$

Equation 2: The cumulative amount of lidocaine released by Lidoderm® 5% patches (Endo Pharmaceuticals) or lidocaine 5% patches (Mylan) at the end of the study arm will be obtained by subtracting residual lidocaine still remaining in the patch at the end of the study arm from the total amount of the drug present in an unused patch.

Further calculation will determine the rate of drug release from the patches using the following equation:

$$Release\ rate = \frac{Lidocaine\ released}{Application\ duration}$$

Equation 3: Determination of lidocaine release rate using the amount of lidocaine released from the patches.

Finally, the lidocaine absorption rate will be calculated using steady state concentrations (C_{ss}) and the clearance (CL) as predicted from the IV bolus data:

$$Absorption\ rate = C_{ss} \times CL$$

Equation 4: Determination of the absorption rate from lidocaine patches using the steady state concentrations and the clearance.

A detailed explanation of the statistics to be performed on the PK analysis is presented in **Section 10.4.**

10.3. Sample Size Consideration

A power analysis determined a sample size of 24 as sufficient for an alpha ≤ .05 to reject the null hypothesis and establish statistical significance. This analysis assumed a 22% within subject variability in the pharmacokinetic parameters, C_{Max} and $AUC_{0-\infty}$, with 80% power. The analysis also assumed that the test and reference formulation vary by 5% and a type-I error rate of 5%.

10.4. Statistical Analysis Plan

Primary statistical analysis will be performed on the natural log transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of lidocaine from the two treatments. The following will be obtained:

- A linear mixed effects model will be used to assess the effects of treatment, period, sequence, and subject within sequence on the natural log transformed $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} of lidocaine. For this, the treatment, period, and sequence effect will be treated as fixed effects (assessed at a significance level of 0.05) while the subject within sequence will be treated as a random effect.
- Intra- and inter-individual variabilities will be obtained.
- The least squares mean estimates for the adjusted differences between treatment means (the log transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) and the standard error associated with these differences will be obtained.
- The 95% confidence intervals for absolute bioavailability of the lidocaine patches will be obtained.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The PI, clinical coordinator, and investigational site will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. The PI and investigational site will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance (QA) reviews, audits, and evaluation of the study safety and progress.

Data collection forms will be used to collect source data. Source data are all information, original records of clinical findings, observations, or other activities in a study. Examples of these original documents and data records include, but are not limited to, data collection forms, laboratory notes, memoranda, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, and subject files and records kept at the pharmacy and at the laboratories involved in the clinical study.

Research records generated in this study will be stored in file cabinets in a locked room and on a secure electronic database. Only authorized personnel at the sites will have access to the data.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The investigational site is responsible for conducting routine QA and quality control (QC) activities to internally monitor study progress and protocol compliance. The PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site. The combined processes of QC and QA form the basis of quality management (QM) and will be applied to this clinical study. QM activities will be guided by each site's Quality Management Plan (QMP). The QMP identifies key indicators (i.e., eligibility, informed consent, concomitant medications, study product, AE/SAE, missed visits, missed labs, etc.) that will be reviewed during quality control checks and quality assurance audits to assess adherence to the IRB-approved protocol, generate quality data, protect data integrity, and safeguard the safety and well-being of study participants.

The study product and accountability records will be maintained at the site and will include the study product shipping receipts, preparation, dispensing, administration, accountability, and destruction records (as applicable).

All staff will have completed the Human Subjects Protection and HIPAA training required by the IRB.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

The PI will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2. Institutional Review Board

The IRB of record for the protocol and consent covered by this grant is the University of Iowa IRB, and approval will be obtained prior to subject enrollment and study initiation. All participating research staff will have undergone documented Human Subjects Protection and HIPAA training. As previously stated, all laboratory data and records will be identified only by code numbers and kept in a locked cabinet.

The study will not be initiated until the IRB provides written or electronic approval of the research plan and the informed consent, and until the PI has provided copies of all appropriate approval documents to the Sponsor. Site activation cannot begin until the Research Involving Human Subjects Committee (RIHSC), the FDA's IRB, has reviewed and approved the study and the approval letter is forwarded to the PI. Appropriate reports on the progress of this study by the PI will be made available to their IRBs and the Sponsor in accordance with applicable government regulations and in agreement with policy established by the Sponsor. The address and contact information for the participating IRB is listed below:

University of Iowa
Hardin Library for the Health Sciences
600 Newton Road, Suite 105
Iowa City, IA 52242
Phone: 319-335-6564
Email: irb@uiowa.edu

13.3. Informed Consent Process

Informed consent is a process that is initiated before the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Consent forms describing in detail the study products, study procedures, and risks are given to the subject and written documentation of informed consent is required before administering any drug product. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, a member of the research team will explain the research study to the subject and answer any questions that the subject has. The subjects will sign the consent document before any study procedures are performed. The subjects will have the opportunity to discuss the study with their surrogates and consider participation before agreeing to enroll in the study.

All subjects must be judged to be capable of signing informed consent by the research team. They must give their written consent to participate in the study. Subjects' questions and concerns will be adequately addressed by the experienced research team prior to signing the consent form. A signed copy of the consent form will be given to the subject for their records, and a signed copy will be placed in their research file. In addition, to assess and document comprehension of the material

presented, a study member will complete a consent checklist to verify that the subject understands all aspects of the study including the procedures and risks. This checklist is IRB-approved and dated and signed by the research staff and made part of the research file.

The subjects may withdraw consent at any time throughout the course of the study. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study or choose to withdraw consent at any time.

With the exception of students, employees and women of childbearing potential who take precautions against pregnancy as defined in the eligibility criteria, special populations will not be enrolled in this study. Examples of special populations are non-English speakers, children, illiterate or non-writing individuals, and prisoners. No individual group will be targeted for enrollment. Every effort will be made to ensure that subjects do not feel there is any secondary gain for themselves from participation.

13.3.1. Informed Consent/Assent Process (in Case of a Minor)

Not applicable.

13.4. Exclusion of Women, Minorities, and Children (Special Populations)

Children under age 18 will be excluded from participation because existing data is insufficient to judge risks in children. Women and minorities will not be excluded. We expect the racial composition of the volunteers in this study to be similar to that in prior recent studies at the University of Iowa.

13.5. Subject Confidentiality

All records of the research will be kept in locked files with subjects' evaluation study materials identified by code only. A separate file will hold the code key. Subjects will not be personally identified in any publications or reports of the study. All blood specimens drawn for research purposes will be identified by code only. The highest standards of subject confidentiality will be kept. Electronic records of data will be kept on password-only accessible computers. Appropriate firewalls and protections of computerized data are maintained to ensure that entry by those other than research personnel is not possible. The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The FDA regulatory authorities may also access subject records. The clinical study site will permit access to such records.

13.6. Study Discontinuation

If the study is discontinued, subjects will not continue with the procedure days or arms. If the study is discontinued, follow-up visits for safety would continue as needed.

13.7. Future Use of Stored Specimens

Back-up serum samples will be stored at the UI College of Pharmacy immediately after collection during the study, and will remain there until after the study is completed. These back-up samples will be aliquots of unused sera collected during the study, and will be stored frozen at -80°C and may be used for future studies. Subjects can decide if they want their samples to be retained for future research or have their samples destroyed at the end of the study. The site may have an option for

subjects to consent to store their specimens with their identification linked or they may choose to de-identify their stored specimens. All future research performed on these specimens must obtain Sponsor authorization and will be approved by the IRB at the University of Iowa. All samples will remain confidential within the extent of state and federal laws. Genetic testing will not be performed.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subject's samples will NOT be kept in their health records, but subject's samples may be kept with the study records or in other secure areas.

14. DATA HANDLING AND RECORD KEEPING

The PI is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All data collection forms will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. Data collection forms will be used and maintained for recording data for each subject enrolled in the study.

14.1. Data Management Responsibilities

The PI and clinical team are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. AEs must be graded and assessed for severity and causality, and reviewed by the PI or MAI.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the PI. During the study, the PI will maintain complete and accurate documentation for the study.

14.2. Data Capture Methods

All data will be entered into an electronic spreadsheet (Microsoft Excel®) and will be reviewed to ensure accuracy and completion prior to data analysis.

14.3. Types of Data

Data for this study will include subject demographic data, safety, and laboratory (lidocaine levels in serum) and drug concentrations in patches post-wear.

14.4. Timing/Reports

After all subjects have completed the procedure days, and laboratory data analyzed, the final report will be prepared.

14.5. Study Records Retention

Records and documents pertaining to the conduct of this study, including case report forms (CRF), data collection forms, and consent forms, must be retained by the PI for at least three years following conclusion of the study or until the FDA authorizes transfer or destruction of study records. No study records will be destroyed without prior authorization from the Sponsor. It is the responsibility of the Sponsor to inform the PI when these documents no longer need to be retained.

14.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or GCP requirements. The noncompliance may be either on the part of the subject, the PI, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. All deviations from the protocol must be addressed in study subject data collection forms. Protocol deviations must be sent to the IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. The Sponsor will identify personnel who will monitor the protocol and identify protocol deviations in addition to the ongoing efforts of study staff. A protocol deviation form will be completed for all deviations. This form will identify the subject by

study ID, the deviation, and possible reasons for the deviation. For deviations that are not subject-specific (e.g. study product, laboratory procedure and storage temperature anomalies) a Non-Subject Specific Protocol Deviation data collection form should be completed.

15. PUBLICATION POLICY

All investigators funded by a government agency must submit to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. This Public Access Policy ensures the public has access to the published results of the funded research. It requires investigators to submit final peer-reviewed journal manuscripts to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication. All publications resulting from this study shall be reviewed by the Sponsor prior to submittal for publication. FDA support will be acknowledged in all publications.

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1. Collinsworth KA, Kalman SM, Harrison DC. The clinical pharmacology of lidocaine as an antiarrhythymic drug. Circulation 1974;50:1217-30.
2. Adinoff B, Devous MD, Sr., Cooper DC, Best SE, Harris TS, Williams MJ. Neural response to lidocaine in healthy subjects. Psychiatry Res 2009;173:135-42.
3. Hamp T, Krammel M, Weber U, Schmid R, Graf A, Plochl W. The effect of a bolus dose of intravenous lidocaine on the minimum alveolar concentration of sevoflurane: a prospective, randomized, double-blinded, placebo-controlled trial. Anesthesia and analgesia 2013;117:323-8.
4. Baik HJ, Kim YJ, Kim JH. Lidocaine given intravenously improves conditions for laryngeal mask airway insertion during propofol target-controlled infusion. Eur J Anaesthesiol 2009;26:377-81.
5. Rowland M, Thomson PD, Guichard A, Melmon KL. Disposition kinetics of lidocaine in normal subjects. Annals of the New York Academy of Sciences 1971;179:383-98.
6. Wallace MS, Laitin S, Licht D, Yaksh TL. Concentration-effect relations for intravenous lidocaine infusions in human volunteers: effects on acute sensory thresholds and capsaicin-evoked hyperpathia. Anesthesiology 1997;86:1262-72.

SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Schedule →		**Arm 1: first patch study**			**Arm 2: Lidocaine hydrochloride injection**	**Arm 3: second patch study**		
Events ↓	**Screen[1]**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Informed Consent	X							
Medical History	X							
Medical History Review		X			X	X		
Physical Exam, weight, height	X							
Targeted physical exam, if indicated		X	X	X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X
12-lead ECG	X							
3-lead ECG					X			
Laboratory tests	X							
Pregnancy serum test[3]	X							
Pregnancy urine test [4]		X			X	X		
Urine drug of abuse screen	X							
Review of all inclusion and exclusion criteria and all laboratory results to ensure subject continued eligibility for the study		X			X	X		
Administration of Lidocaine (Topical or Injection)		X			X	X		
Concomitant medications review		X	X	X	X	X	X	X
Patch adhesion assessment		X				X		
Pharmacokinetic blood samples [5]		X	X	X	X	X	X	X
Adverse events monitoring - systemic		X	X	X	X	X	X	X
Adverse events monitoring - local: Primary Skin Irritation (PSI)		X	X	X		X	X	X

[1] Screening will be conducted for every volunteer to ensure eligibility

[2] Vital signs include blood pressure, temperature, pulse, and respiration rate

[3] Serum pregnancy test for all women of childbearing potential

[4] Urine pregnancy test for all women of childbearing potential if it has been >30 days since serum pregnancy test.

[5] For each patch study arm: A pre-dose sample will be obtained within 60 min pre-patch application and then at 1:00, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00, 24:00, 27:00, 30:00, 33:00, 36:00, 39:00, and 48:00 hr post-patch application

For IV study arm: 5 A blood sample will be collected within 60 minutes pre-IV injection and then at 00:02, 00:05, 00:10, 00:20, 00:30, 00:45, 1:00, 2:00, 3:00, 4:00, 6:00, 8:00, 10:00 hours post IV injection

APPENDIX B: ACCEPTABLE SCREENING VALUES & LABORATORY REFERENCE RANGES

Laboratory Test	Acceptable Value per University of Iowa Pathology Handbook	Units
White Blood Cell count (WBC)	3.7 – 10.5	k/mm^3
Hemoglobin	13.2-17.7 (males)	g/dL
	11.9-15.5 (Females)	g/dL
Hematocrit	40-52 (Males)	Percent
	35-47 (Females)	Percent
Platelet count	150-400	k/mm^3
Sodium	135–145	meq/L
Potassium	3.5 – 5.0	meq/L
Creatinine	0.6 – 1.2 (Males)	mg/dL
	0.5 – 1.0 (Females)	mg/dL
AST	0 – 40 (Males)	Unit/L
	0 – 32 (Females)	Unit/L
ALT	0 – 41(Males)	Unit/L
	0 – 33 (Females)	Unit/L
Chloride	95 – 107	mEq/L
Bicarbonate	22 – 29	mEq/L
BUN	10 – 20	mEq/L
Serum β-HCG	Negative	*n/a*
Urine pregnancy test	Negative	*n/a*
Urine Drug (toxicology)	Must be negative for cocaine, opiates, and barbiturates	
Electrocardiogram (ECG)	Must <u>not</u> have any of the following, in order to be acceptable: Pathologic Q wave abnormalities Significant ST-T wave changes Left ventricular hypertrophy Right bundle branch block Left bundle branch block Advanced A-V heart block Non-sinus rhythm, excluding isolated premature atrial contractions	

n/a, not applicable

APPENDIX C: TOXICITY GRADING SCALES

Vital Signs*	Reference Range of Normal Values	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever (°C)** (°F)	35-37.9 95-100.3	38.0-38.4 100.4-101.1	38.5- 38.9 101.2-102.0	39.0-40 102.1-104	>40 >104
Tachycardia - beats per minute	55-100	101-115	116-130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute	55-100	50- 54	45- 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	90 – 139	140 – 159	160 – 179	>180	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	60 – 89	90 – 99	100 – 110	>110	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg ***	90-139	85-89	80-84	< 80	Mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Respiratory Rate - breaths per minute	12-17	18-20	21- 25	>25	Intubation

*Subject should be at rest for all vital sign measurements
**Oral temperature; no recent (30 min) hot or cold beverages
***A low diastolic blood pressure reading will be assessed to determine whether there are associated signs and symptoms

APPENDIX C: TOXICITY GRADING SCALE (CON'T)

TOXICOLOGY GRADING SCALE – SYSTEMIC

	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema	Anaphylaxis
Headache	Mild discomfort that is brief or easily tolerated	Discomfort that causes mild to moderate limitation in activity	Symptom prevents all normal activity for 24 hours or more	ER visit or hospitalization
Fatigue	Normal activity reduced	Normal activity decreased 25-0%	Can't go to work or school	ER visit or hospitalization
Any other illness or clinical adverse event	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

APPENDIX D: ADHESION ASSESSMENT SCORING

Score	Condition
0	≥ 90% adhered (essentially no lift off the skin)
1	≥ 75% to < 90% adhered (some edges only lifting off the skin)
2	≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)
3	> 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4	0% adhered - transdermal system detached (patch completely off the skin)