EVALUATION OF THE BIOAVAILABILITY OF LIDOCAINE DERMAL PRODUCTS

Short title: PK and DPK of lidocaine dermal products

UMB IRB #: HP-00067033

Principal Investigator:

Audra L. Stinchcomb (contact), PhD, RPh

Medically Accountable Investigator(s):

Jeffrey Fink, MD, MS

Shoshana Weiner, MD, MPH

Sponsor:

Food and Drug Administration
Office of Generic Drugs

NCT03145207

Version 13.0

11 December 2018

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) and the applicable Food and Drug Administration 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.

Protocol Summary

Title:	Evaluation of the bioavailability of lidocaine dermal products
Population:	Healthy adults age 18 - 45 years
Number of Sites:	Single site: University of Maryland School of Medicine
Study Duration:	Approximately up to 1 year
Subject Participation Duration:	Approximately 16-18 weeks including the screening period
Description of Study Product:	Lidocaine (Lidoderm® patch) 5%, Endo Pharmaceuticals; Lidocaine 5% patch, Mylan
Objective:	The present study aims to generate human dermatopharmacokinetics (DPK) and pharmacokinetic (PK) data in healthy subjects for the purpose of establishing a reference for *in vitro-in vivo* correlation (IVIVC) with an in vitro model following the application of lidocaine formulations: Lidoderm® (Lidocaine 5%patch) and lidocaine 5% Mylan patch with and without heat application.
Description of Study Design:	The study will be an open-label, study over 16-18 weeks (n=12 healthy subjects) with one week washout period between procedure days. • The study contains eight procedure days: • **Procedure Day 1:** Lidoderm® patches containing 5% lidocaine to be worn for 10 h. • **Procedure Day 2:** Mylan Lidocaine patches containing 5% lidocaine to be worn for 10 h. • **Procedure Day 3:** The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30 minutes, 4 hours after application of the Lidoderm® patches. • **Procedure Day 4:** The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30 minutes, 8.5 hours after application of the Lidoderm® patches. • **Procedure Day 5:** The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30

minutes, 4 hours after application of the Mylan (lidocaine) patches (5%).

- **Procedure Day 6:** The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30 minutes, 8.5 hours after application of the Mylan (lidocaine) patches (5%).

- **Procedure Day 7:** Multiple applications of Lidoderm® patch pieces, Mylan lidocaine 5% patch pieces; Removal of patch pieces at 10 h, followed by tape stripping (Uptake or Absorption); Tape stripping at 15 h [5 h after patch piece removal] (Clearance)

- **Procedure Day 8:** Tape stripping at 24 h [14 h after patch piece removal] (Clearance)

A) Pharmacokinetics (PK)

Each subject will be his/her own control and each subject will sign an institutional review board–approved consent form explaining the purpose, nature, risks, benefits, and duration of the study. The study will be conducted in accordance with good clinical practice guidelines and with the ethical principles originating in the Declaration of Helsinki.

The subject's skin in the area of application (volar forearms and upper arm(s)) will be relatively free of hair before patch application. Blood samples (approximately 3 mL each) will be drawn in BD vacutainer (BD # 366668) tubes. On Procedure Days 1-6, blood samples will be obtained as follows:

- Within 60 min pre-patch application and then up to 10 hours, during wear and post patch removal (from 10 hours to 15 hours). No blood samples will be obtained during the DPK study (Procedure Days 7 and 8).

B) Dermatopharmacokinetics (DPK) of Lidocaine Patches

- Lidocaine products (6 sites/product, 3 sites/arm/product) will be applied to each arm. All of the patchpieces will be removed at 10 h. Four patch sites will be tape stripped (uptake or absorption) at 10 h, four patch sites (two sites/product/time point) will be tape stripped (clearance) at 15 and 24 h.

- Tape strips applied and removed after patch piece removal to determine the drug concentration in stratum corneum, which is the outer barrier layer of the epidermis.

C) Residual Drug Analysis of Lidocaine Patches

In conjunction with the above described study, residual drug analysis will also be conducted for the used patches described in Part A.

- Prior to administration to the Subject as described in Part A, patches will be weighed and the weight recorded.

- The pouch, release liner and all items coming into contact with the patches (gloves, forceps, etc..) applied in Part A will be retained for analysis.

- The used patches will be retained for drug content analysis.

- All items coming into contact with the patches during removal from the Subject will be stored in a separate labeled Ziploc bag until analyzed for drug content.

1 KEY ROLES

U01 Principal Investigator:

Audra L. Stinchcomb (contact), PhD, RPh
Professor
Department of Pharmaceutical Sciences
University of Maryland School of Pharmacy
20 N Pine St, Room PHN521
Baltimore, MD 21201
Phone: 410-706-2646
Fax: 410-706-0886
Email: astinchc@rx.umaryland.edu

Medically Accountable Investigator(s)

Jeffrey C Fink M.D., M.S.
Professor
Department of Medicine and Epidemiology (secondary)
University of Maryland School of Medicine
UMMC, Room NN3E03
Baltimore, MD 21201
Phone: 410-328-4822
Fax: 410-328-5685
Email: jfink@medicine.umaryland.edu

Shoshana Weiner, M.D., MPH
Associate Professor
Department of Medicine
UMMC, Room N3E10
Baltimore, MD 21201
Phone : 667-214-1500
Cell : 443-799-001
Email : ssnitker@medicine.umaryland.edu

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The purpose of this project is to investigate the development of appropriate methods to determine the in vitro/in vivo correlation (IVIVC) of drug absorption from dermal products, which has represented a longstanding challenge. The model drug for this study is lidocaine, which is available in two different patch formulations approved by the United States FDA. This healthy human subject study will provide the carefully designed protocols and data for direct comparison (IVIVC) with an in vitro human skin diffusion study model. Generic drugs are approved based upon bioequivalence (BE) testing, and with respect to oral drug delivery, the accepted BE approach is relatively straightforward and is principally based on matching blood level profiles. In some cases, in vitro dissolution tests can be done to help determine the bioequivalence of an oral dosage form. For topical drug products in the United States, with the exception of the corticosteroids and a few other products, a comparative clinical endpoint study is often necessary for approval of a generic product or for replacement of an approved dermatological drug product with one that has major changes. Comparative clinical trials are relatively insensitive, time-consuming and costly. It is especially difficult to gain the adequate statistical power needed to evaluate bioequivalence in some dermatological conditions, and can require a large number (i.e., hundreds[1,2]) of subjects.

This study supports FDA's continuing effort to identify the most accurate, sensitive, reproducible and efficient methods to evaluate topical dermatological drug products.

2.2 Rationale

The goal of this study is to help establish more efficient pathways for approval of topical generic drug products by developing better tools to assess bioavailability. This study with the reference listed drug (RLD) Lidoderm® (lidocaine 5%) topical patch and its approved generic product marketed by Mylan will provide sufficient systemic concentrations of lidocaine to characterize the systemic bioavailability. The systemic concentration will be compared with the local bioavailability of lidocaine in the skin using the same products, measured by tape-stripping the skin to measure the concentrations of lidocaine in the stratum corneum. The same RLD and generic topical patches will also be studied (under a parallel but separate in vitro study protocol) using an in vitro permeation test (IVPT) model with excised human skin which has demonstrated IVIVC in previous studies. This research will help establish whether the IVPT model correlates with and is predictive of in vivo bioavailability, and whether IVPT and/or in vivo tape-stripping can be utilized as part of a collective weight-of-evidence approach to support an approval pathway for generic topical drug products. In addition, *in vivo* studies will be conducted to compare

the influence of heat on patch products (RLD e.g. Lidoderm® versus generic product e.g. Mylan lidocaine 5% patch) that have different inactive ingredients.

Lidoderm® patch and Mylan lidocaine 5% patch

	Lidoderm® 5% patch	**Lidocaine 5% patch**
Inactive ingredients	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	polyisobutylene adhesive matrix
Formulation	Patch	Patch
Manufacturer	Endo Pharmaceuticals	Mylan

3 OBJECTIVES

3.1 Study Objectives

The present study aims to:

1) Generate human PK data for the purpose of establishing an IVIVC model by collecting data following the application of two lidocaine formulations: Lidoderm® (lidocaine 5% patches) and Mylan lidocaine 5% patches.
2) Generate DPK data for the purpose of establishing a fundamental IVIVC model by collecting skin concentration data following the application of two lidocaine formulations: Lidoderm® (lidocaine 5% patches) and Mylan lidocaine 5% patches.
3) Determine serum lidocaine levels after using RLD (Lidoderm®, matrix type patch, Endo Pharmaceuticals) and generic lidocaine (Mylan) patch with and without standardized heat application in healthy adult subjects. The influence of heat on RLD vs. generic product that are formulated differently impose critical safety issue for users of generic patches.

3.2 Study Outcome Measures

For the DPK study the main outcome measure is the ratio of clearance and uptake of lidocaine drug concentrations for each lidocaine formulation. For the PK study the main outcome measure is the maximum serum concentration (C_{max}); time of maximum serum concentration (T_{max}) of lidocaine and area under the curve (AUC) attained with and without heating for Lidoderm® patch and Mylan lidocaine 5% patch. In addition, we will determine residual drug content from worn Lidoderm® patches and Mylan lidocaine 5% patches to estimate total amount of absorbed lidocaine from each.

4 STUDY DESIGN

This is designed as an open-label, non-placebo controlled study. The products tested are already FDA approved; however, the products are used outside of the approved indications by using healthy subjects. The products being tested are for research purposes only; this is not a treatment study. The study is not blinded because PK and DPK assessment is not subject to participant and/or observer bias. The study will consist of seven Study Sessions (12 healthy subjects). Each of the 12 subjects will be enrolled to complete seven study sessions (eight procedure days). There will be no overnight stays during the study. There will be at least a one week washout period between each study session.

The studies are as follows:

STUDY SESSION 1
(Procedure Day 1): Lidoderm® patches [140 cm^2 each] will be applied for 10 h and removed. Blood samples will be collected at specified times over a 16 hour period of the clinical study. There will be at least a one week washout period before proceeding to the next Study Session.

STUDY SESSION 2
(Procedure Day 2): Mylan lidocaine 5% patches [140 cm^2 each] will be applied for 10 h and removed. Blood samples will be collected at specified times over a 16 hour period of the clinical study. There will be at least a one week washout period before proceeding to the next Study Session.

STUDY SESSION 3
(Procedure Day 3): Lidoderm® (lidocaine) [140 cm^2 each] will be applied without heat for 4 hours, then heating pad(s) will be applied over each patch (see details in Manual of Procedures (MOP)) and set to induce a skin temperature of 42.0 ± 4°C for 1 hour 30 minutes then heating pad(s) are removed, and the patches will be kept on, then removed (patches applied for a total of 10 hours). Blood samples will be collected at specified times over a 16 hour period of the clinical study. There will be at least a one week washout period before proceeding to the next Study Session.

STUDY SESSION 4

(Procedure Day 4): Lidoderm® (lidocaine) patches [140 cm^2 each] will be applied without heat for 8.5 hours, then heating pad(s) will be applied over each patch and set to induce a skin temperature of 42.0 ± 4°C for 1 hour 30 minutes, then the patches and heating pad(s) will both be removed (patches applied for a total of 10 hours). Blood samples will be collected at specified times over a 16 hour period of the clinical study. There will be at least a one week washout period before proceeding to the next Study Session.

STUDY SESSION 5

(Procedure Day 5): Mylan 5% lidocaine patches [140 cm^2 each] will be applied without heat for 4 hours, then theratherm® heating pad(s) will be applied over each patch and set to induce a skin temperature of 42.0 ± 4°C for 1 hour 30 minutes, then removed (patches applied for a total of 10 hours). Blood samples will be collected at specified times over a 16 hour period of the clinical study. There will be at least a one week washout period before proceeding to the next Study Session.

STUDY SESSION 6

(Procedure Day 6): Mylan 5% lidocaine patches [140 cm^2 each] will be applied without heat for 8.5 hours, then heating pad(s) will be applied over each patch and set to induce a skin temperature of 42.0 ± 4°C for 1 hour 30 minutes, then the patches and the heating pad(s) will both be removed (patches applied for a total of 10 hours). Blood samples will be collected at specified times over a 16 hour period of the clinical study. There will be at least a one week washout period before proceeding to the next Study Session.

STUDY SESSION 7

(Procedure Day 7): Six sites (3 sites/arm) will be designated on the volar forearms for each lidocaine formulation and 1 site for a negative control. Lidoderm® 5% patch pieces and Mylan lidocaine 5% patch pieces will be applied. At 10 h post application, all formulations will be removed from their respective sites. Two sites for each patch product will be tape stripped at the designated uptake (absorption) time. Two sites for each formulation will be tape stripped at the designated clearance period.

(Procedure Day 8): The remaining two sites for each formulation will be tape stripped at the designated clearance period.

5 STUDY ENROLLMENT AND WITHDRAWAL

Only adult healthy volunteers who meet the inclusion/exclusion criteria will be eligible for enrollment into this study. Twelve subjects will be recruited as well as at least another five alternates who could replace subjects who drop out from the study for any unforeseen reason. The study population selected for this study includes healthy adult men and women without other comorbidities ages 18-45, inclusive. The selection criteria are designed to exclude people who might have medical conditions that could pose a safety risk and people whose medical conditions might interfere with the objectives and results of the study.

Subjects will be recruited by local advertisements 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 a screening and informed consent form. Each of the 12 subjects enrolled will be expected to complete all study sessions.

We aim to target at least 40% participants of each gender. There are no specific ethnicity/race categories recruitment targets although such information will be recorded by the researchers.

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 who are of any ethnic background between the age of 18 and 45 years old.

2. Subjects must be non-smokers (must have refrained from the use of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, patches or electronic cigarettes) over the previous 2 months and are not currently using tobacco products.

3. Provide written informed consent before initiation of any of the study procedures.

4. Agrees not to participate in another clinical trial/study or to participate in an investigational drug study for at least 1 month after the last study session.

5. Able to adhere to the study restrictions and protocol schedule.

6. Able to participate in all study sessions.

7. Has a volar forearm of either at least 24 cm (9.45 inches) in length or of sufficient size that can accommodate the formulations to be tested in a study area that begins at least 5 cm (1.97 inches) above the wrist and ends a minimum of 0.5 cm (0.197 inches) below the antecubital fossa (i.e., the bend in the arm at the elbow).

8. Subjects have upper arms (minimum 28 cm (11 inch) circumference) large enough to allow for the placement of two 140 cm^2 patches on one upper arm or one 140 cm^2 patch on each upper arm.

9. Subjects deemed to be healthy as judged by the MAI and determined by medical history, physical examination and medication history.

10. Negative urine drug screening test.

11. Have normal screening laboratories for WBC, CBC, Hgb, platelets, sodium, potassium, chloride, bicarbonate, BUN, creatinine, ALT and AST.

12. Have normal screening laboratories for urine protein and urine glucose.

13. Female subjects must be of non-childbearing potential (as defined as surgically sterile [i.e., history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year), or if of childbearing potential must be non-pregnant at the time of enrollment and on the morning of each procedure day, and must 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 donate blood to a blood bank throughout participation in the study and at least 3 months after the last procedure day.

15. Have a normal ECG; must not have the following to be acceptable: pathologic Q wave abnormalities, significant ST–T wave changes, left ventricular hypertrophy, right bundle branch block, left bundle branch block. (sinus rhythm is between 55–100 beats per minute).

16. Have normal vital signs:
    - Temperature 35-37.9°C (95-100.3°F)
    - Systolic blood pressure 90-140 mmHg
    - Diastolic blood pressure 60-90 mmHg
    - Heart rate 55-100 beats per minute
    - Respiration rate 12-20 breaths per minute

5.2 Subject Exclusion Criteria

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

1. Women who are pregnant, lactating, breast feeding or have a positive serum pregnancy test at enrollment or positive urine pregnancy test on the morning of each study session.
2. Smokers (current use or use over the previous 2 months of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, patches or electronic cigarettes).
3. Participation in any ongoing investigational drug trial/study or clinical drug trial/study.
4. History of chronic obstructive pulmonary disease or cor pulmonale, or substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression.
5. Active positive Hepatitis B, C and/or HIV serologies (see *Appendix B*).
6. Known anemia.
7. Positive urine drug screening test.
8. Use of any prescription medication during the period 0 to 30 days; or over-the counter medication (e.g. antihistamines or topical corticosteroids) and short term (<30 days) prescription medications during the period 0 to 3 days before a study session (vitamin, herbal supplements and birth control medications not included).
9. Donation or loss of greater than one pint of blood within 60 days of entry to the study.
10. Any prior adverse reaction to lidocaine. Hypersensitivity to lidocaine, known history of hypersensitivity to local anesthetics of the amide type, other excipients in the patches tested or to adhesives on tapes used to cover or tape strip treatment sites.
11. Received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within 1 month before enrollment in this study or expects to receive an experimental agent during the study.
12. Any condition that would, in the opinion of the Medically Accountable Investigator (MAI), place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
13. Consumption of alcohol within 24 h prior to dose administration.

14. History as either reported by the subject or evident to the investigator of infectious disease or skin infection or of chronic skin disease (e.g., diabetes, psoriasis, atopic dermatitis).

15. Hereditary skin disorders or any skin inflammatory conditions as reported by the research participant or evident to the MAI.

16. History of significant dermatologic cancers (e.g., melanoma, squamous cell carcinoma) except basal cell carcinomas that were superficial and did not involve the investigative sites.

17. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at application site (volar forearms/upper arms), sunburn, raised moles and scars, open sores at application site (volar forearms/upper arms), scar tissue, tattoo or coloration that would interfere with placement of formulations, skin assessment or reactions to lidocaine.

18. BMI $\geq$ 30 kg/m^2.

6 STUDY PRODUCT

6.1 Study Product Description

6.1.1 Lidoderm® (lidocaine 5%) patch [140 cm^2]

Lidoderm® is a prescription lidocaine-containing patch that releases lidocaine through the skin into the body. The patch releases lidocaine over a 12 h period, the recommended duration of patch application. The patch is indicated to relieve the pain of post-herpetic neuralgia [after-shingles pain].

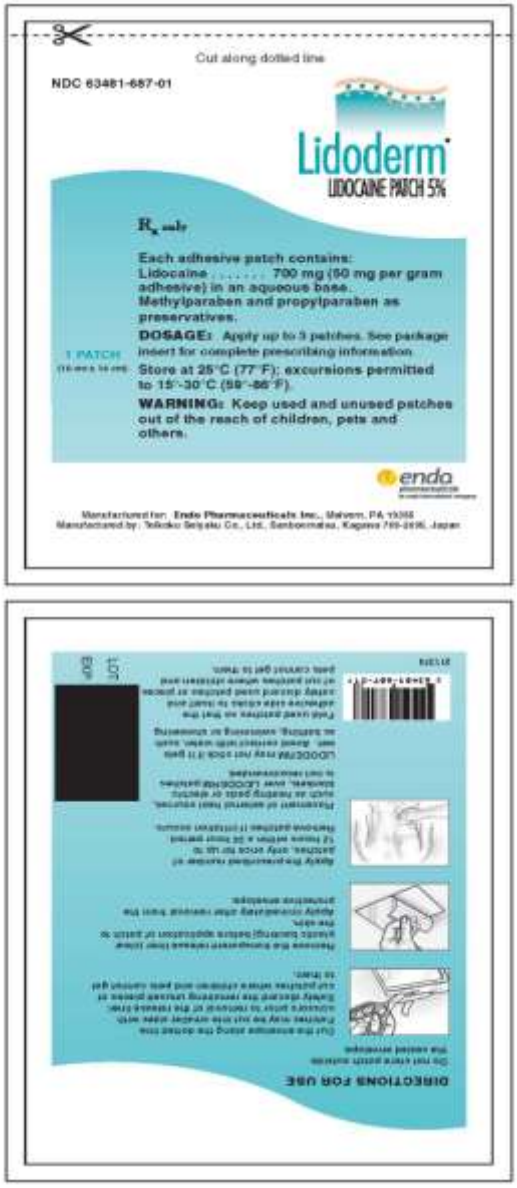
6.1.2 Mylan (lidocaine 5%) patch [140 cm^2]

Mylan lidocaine 5% patch is a prescription lidocaine-containing patch that releases lidocaine through the skin into the body. The patch releases lidocaine over a 12 h period, the recommended duration of patch application. The patch is indicated to relieve the pain of post-herpetic neuralgia [after-shingles pain].

6.2 Formulation, Packaging, and Labeling

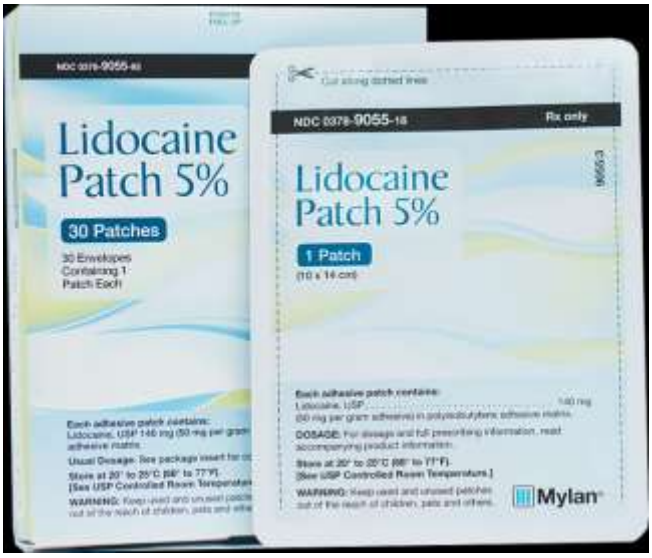
6.2.1 Lidoderm® (5% lidocaine) patch [140 cm^2]

Active ingredient (in each patch): Lidocaine, 700 mg (50 mg per gram adhesive) in an aqueous base. 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 patch is manufactured by Endo Pharmaceuticals Inc. This product should be stored at room temperature.



6.2.2 Mylan 5% lidocaine patch [140 cm^2]

Active ingredient (in each patch): Lidocaine, 140 mg USP (50 mg per gram adhesive) in a polyisobutylene adhesive matrix. This patch is manufactured by Mylan Pharmaceuticals Inc. This product should be stored at room temperature.


Lidocaine
Patch 5%
30 Patches
30 Envelopes
Containing 1
Patch Each
NDC 0378-9055-18
Rx only
Lidocaine
Patch 5%
1 Patch
(10 x 14 cm)
Mylan

7 PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

7.1 Study Hypothesis

DPK and PK

We will test the null hypothesis (H_0) that the mean clearance/uptake lidocaine amount ratio, and the PK parameters (Cmax and AUC) between the lidocaine patch products are different (i.e., outside the 80–125% range).

Heat

Due to differences in inactive ingredients between RLD and generic lidocaine patches, the release rate of lidocaine may differ from these patches upon exposure to heat. As a result, in this study the influence of standardized heat application (two heat periods) on the pharmacokinetics (PK) parameters of lidocaine will be studied after using Lidoderm® (reference) and Mylan lidocaine (generic) patches. Analysis will be to determine whether heat differentially impacts lidocaine serum concentrations between Lidoderm® (reference) and Mylan (lidocaine) patches. We will test the null hypothesis (H_0) that the coefficient for the patch-by-heat interaction equals zero, adjusting for time.

7.2 Analyses

Lidocaine concentrations will be measured in serum samples collected from each subject. Blood samples (approximately 3 mL (0.6 tsp)) will be collected during the Study Sessions 1, 2, 3, 4, 5 and 6. During Study Session 1 and 2 within 60 min before dosing and then at 2 hours, 3 hours, 3 hours 55 minutes, 4 hours 50 minutes, 5 hours 30 minutes, 6 hours, 6 hours 30 minutes, 7 hours, 8 hours 25 minutes, 9 hours 20 minutes, 10 hours, 10 hours 30 minutes, 11 hours, 11 hours 30 minutes, 12 hours, 13 hours, 14 hours and 15 hours post-patch application. Blood samples (approximately 3 mL (0.6 tsp)) will be collected during Study Sessions 3 and 5 within 60 min before dosing and then at 2 hours, 3 hours, 3 hours 55 minutes, 4 hours 5 minutes, 4 hours 20 minutes, 4 hours 35 minutes, 4 hours 50 minutes, 5 hours 5 minutes, 5 hours 30 minutes, 6 hours, 6 hours 30 minutes, 7 hours, 8 hours 25 minutes, 9 hours 20 minutes, 10 hours, 10 hours 30 minutes, 11 hours, 11 hours 30 minutes, 12 hours, 13 hours, 14 hours and 15 hours post-patch application. Blood samples (approximately 3 mL (0.6 tsp)) will be collected during Study Sessions 4 and 6 within 60 min before dosing and then at 2 hours, 3 hours, 3 hours 55 minutes, 4 hours 50 minutes, 5 hours 30 minutes, 6 hours, 6 hours 30 minutes, 7 hours, 8 hours 25 minutes, 8 hours 35 minutes, 8 hours 50 minutes, 9 hours 5 minutes, 9 hours 20 minutes, 9 hours 35 minutes, 10 hours, 10 hours 30

minutes, 11 hours, 11 hours 30 minutes, 12 hours, 13 hours, 14 hours and 15 hours post-patch application. DPK will be conducted at 10 h (skin drug uptake) or 5 h and 14 h (skin drug clearance) post patch application. Non compartmental analyses (NCA) will be conducted to estimate the PK parameters such as: maximum serum concentration (Cmax); apparent elimination rate constant (k); apparent half-life ($t_{1/2}$), calculated as 0.693/k; $AUC_{0\text{-}last}$ of the serum concentration–time determined by the linear trapezoidal method; and AUC value extrapolated to infinity (AUC_{inf}), calculated as the sum of $AUC_{0\text{-}last}$ and the area extrapolated to infinity: $AUC_{inf} = AUC_{0\text{-}last} + C_{last}/k$ where C_{last} would be the last quantifiable concentration. All NCA analyses will be conducted using Phoenix® WinNonlin® 6.4 (Pharsight, a Certara Company, CA).

7.3 Final Analysis Plan

An objective of this study is to determine PK parameters (C_{max}, AUC and ratio of stratum corneum drug concentration during uptake and clearance) of lidocaine in healthy adults and DPK data after using Lidoderm® (lidocaine 5% patches) and Mylan 5% lidocaine patches for the purpose of IVIVC by collecting data over two separate periods. Complimentary *in vitro* data will be collected using human skin.

Secondly the objective is to investigate the influence of heat application on the PK parameters of lidocaine after using a RLD and generic patches along with no heat application. The primary PK parameters to be compared are 1) Cmax, before and after heat application and 2) AUC before and after heat application consistent with similar PK studies[13-23]. Analysis of variance (ANOVA) followed by post-hoc Bonferroni test will be used for comparing the differences in the means of the PK parameters and significant differences will be declared at $p<0.05$. The statistical comparisons will be conducted as follow:

If lidocaine PK concentrations are found to be non-normally distributed, then we will examine Box-Cox transformations (e.g., log, square-root, etc.) that can achieve normality. If no transformation can achieve normality, then will use permutation tests to compute empirical *p*-values, and will use the bootstrap to compute standard errors and confidence intervals that account for within-person correlation.

IVIVC will be conducted comparing PK parameters and profiles to predicted PK parameters and profiles using IVPT and *in vitro* DPK results. Multiple methods will be implemented to develop an IVIVC. The first method is to compare the steady state concentrations. The predicted steady state concentration using our current IVPT data will employ the following formula:

$$C_{ss} = \frac{J_{ss} * A}{CL}$$

The second method will compare the PK profiles of the clinical and IVPT study by predicting lidocaine concentrations at each time point in the IVPT study and comparing it to the clinical PK profile. The third method will be to determine and compare residual patch analysis between *in vitro* and *in vivo*.

In terms of developing an IVIVC for the DPK study a comparison will be made between *in vitro* and *in vivo* uptake and clearance lidocaine amounts. The second method is to compare the clearance to uptake lidocaine amount ratio between *in vitro* and *in vivo*.