EVALUATION OF THE BIOAVAILABILITY OF METRONIDAZOLE DERMAL PRODUCTS

Short title: PK of metronidazole dermal products

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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 metronidazole 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 10 weeks including the screening period
Description of Study Product:	Metronidazole topical gel, 0.75%, Prasco Laboratories; Metronidazole topical gel, 0.75%, Impax Laboratories; Metronidazole topical cream, 0.75%, Fougera Laboratories.
Objective:	The present study aims to study the systemic bioavailability of metronidazole in healthy volunteers following the application of topical metronidazole products: metronidazole topical gel, 0.75% (RLD), metronidazole topical gel, 0.75% (generic) and metronidazole topical cream, 0.75% (generic). The metronidazole gel, 0.75% products are therapeutically equivalent. The metronidazole cream, 0.75% will be used as an inequivalent control for the study. The pharmacokinetic data obtained in this study will be used in combination with in vitro data collected elsewhere to develop an in vitro in vivo correlation that could be leveraged to evaluate bioequivalence of generic metronidazole topical drug products.
Description of Study Design:	The study will be an open-label, crossover study over 10 weeks (n=12 healthy subjects) with one week washout period between studies. The study contain six procedure days: • **Procedure Day 1:** RLD topical gel containing 0.75% metronidazole to be applied for 25 h. Blood samples obtained on **Procedure Day 1 and 2**. • **Procedure Day 3:** Generic topical gel containing 0.75% metronidazole to be applied for 25 h. Blood samples

obtained on **Procedure Day 3 and 4**.

- **Procedure Day 5:** Generic topical cream containing 0.75% metronidazole to be applied for 25 h. Blood samples obtained on **Procedure Day 5 and 6**.

A) Pharmacokinetics

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 (upper arm) will be relatively free of hair before gel or cream application. Blood samples (approximately 5 mL (1 tsp) each) will be drawn in BD vacutainer tubes. On Procedure Day 1, 2, 3, 4, 5 and 6, blood samples will be obtained as follows:

- Within 60 min pre-gel/cream application and then during wear, up to 25 h.

1 KEY ROLES

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Schematic of Study Design
n=12 subjects

Study Session 1
[Procedure Day 1 and 2]

Product:	**Metronidazole gel, 0.75% (RLD)**
Time of admission:	**Morning of Procedure Day 1**
Time of application:	**Morning of Procedure Day 1**
Duration of application:	**25 h**
Sampling:	**26 hours**
Sampling time points:	**-60 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 23, 24, 25 h**

Washout period at least 1 week

Study Session 2
[Procedure Day 3 and 4]

Product:	**Metronidazole gel, 0.75% (generic)**
Time of admission:	**Morning of Procedure Day 3**
Time of application:	**Morning of Procedure Day 3**
Duration of application:	**25 h**
Sampling:	**26 hours**
Sampling time points:	**-60 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 23, 24, 25 h**

Washout period at least 1 week

Study Session 3
[Procedure Day 5 and 6]

Product:	**Metronidazole cream, 0.75% (generic)**
Time of admission:	**Morning of Procedure Day 5**
Time of application:	**Morning of Procedure Day 5**
Duration of application:	**25 h**
Sampling:	**26 hours**
Sampling time points:	**-60 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 23, 24, 25 h**

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

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 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 for 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.

The model drug for this study is metronidazole, which is available in different topical formulations, gel, cream and lotion, approved by the United States FDA. The metronidazole gels and cream have been chosen for this study because the therapeutically equivalent metronidazole gels will be used to evaluate BE in vivo. The metronidazole cream is being used as the non-BE control for this project.

2.2 Rationale

The goal of this study is to help establish more efficient pathways for approval of topical drug products by developing better tools to assess bioavailability. This study with a RLD and generic metronidazole topical gel, 0.75% and generic metronidazole topical cream, 0.75% will provide sufficient systemic concentrations of metronidazole to characterize the systemic bioavailability. The same products 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. The IVPT model has demonstrated IVIVC in previous studies using different drug molecules and formulations. This research will help establish whether the IVPT model correlates with and is predictive of in vivo bioavailability, and whether IVPT can be utilized as part of a collective weight-of-evidence approach to support an approval pathway for topical drug products.

These coordinated evaluations also collectively provide the in vivo reference datasets that are needed to establish IVIVC for the IVPT model which may then be utilized to support a new pathway for approval of numerous topical drug products for patients.

Metronidazole topical products

	Metronidazole gel, 0.75% (RLD) NDC: 66993-962-45	**Metronidazole gel, 0.75% (generic) NDC: 0115-1474-46**	**Metronidazole cream, 0.75% (generic) NDC: 0168-0323-46**
Inactive ingredients	0.8 mg of methylparaben and 0.2 mg of propylparaben as preservatives in a gel consisting of carbomer 940, edetate disodium, propylene glycol, purified water and sodium hydroxide	Carbopol 980, edetate disodium, methylparaben, propylene glycol, propylparaben, purified water and sodium hydroxide	Emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid, sodium hydroxide and purified water
Formulation	topical gel	topical gel	topical cream
Manufacturer	Prasco Laboratories	Impax Generics	Fougera Laboratories

3 OBJECTIVES

3.1 Study Objectives

1) Generate human PK data by collecting data following the application of three metronidazole formulations: RLD and generic metronidazole gel, 0.75% and generic metronidazole cream, 0.75%. This data will be used to assess the bioequivalence of these products or lack thereof.

2) To develop in vitro/in vivo correlation (IVIVC) models for dermal products. PK data from this study as well as in vitro data collected elsewhere from IVPT studies will be used to develop IVIVC models which could provide a surrogate for conducting clinical endpoint studies (required to demonstrate bioequivalence of dermal products).

3.2 Study Outcome Measures

For the PK study the main outcome measure is the maximum serum concentration (C_{max}), time of maximum serum concentration (T_{max}) of metronidazole and area under the curve (AUC) attained from RLD and generic metronidazole gel, 0.75% and generic metronidazole cream, 0.75%.

4 STUDY ENROLLMENT AND WITHDRAWAL

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

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

4. Agree not to participate in another clinical trial/study during the study period 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 protocol schedule and study restrictions.
6. Able to participate in all study sessions.

7. Subjects have upper arms large enough to allow for the placement of 200 cm^2 [31 in^2] area for application of gels or cream.

8. Subjects deemed to be healthy as judged by the Medically Accountable Investigator (MAI) and determined by medical history, physical examination and medication history.

9. Negative urine drug screening test (cannabinoids, amphetamines, barbiturates, benzodiazepine, cocaine, methadone, opiates, PCP).
10. Have normal screening laboratories for WBC, Hgb, platelets, sodium, potassium, chloride, bicarbonate, BUN, creatinine, ALT and AST.
11. Have normal screening laboratories for urine protein and urine glucose.
12. 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 reliable hormonal or barrier birth control such as implants, injectables, combined

oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner.

13. Agrees not to donate blood to a blood bank throughout participation in the study and at least 3 months after the last study session.
14. 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).
15. Have normal vital signs:
    - Temperature 35-37.9°C (95-100.3°F)
    - Systolic blood pressure 90-165 mmHg
    - Diastolic blood pressure 60-100 mmHg
    - Heart rate 55-100 beats per minute
    - Respiration rate 12-20 breaths per minute

4.2 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/tobacco users (current use or use over the previous 2 months of nicotine-containing substances (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, patch or electronic cigarettes).
3. Participation in any ongoing investigational drug trial/study or clinical drug trial/study.
4. History as either reported by the subject or evident to the Medically Accountable Investigator (MAI) of infectious disease or skin infection or of chronic skin disease (e.g., psoriasis, atopic dermatitis).
5. History of diabetes.
6. 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.
7. Body Mass Index (BMI) ≥30 kg/m^2.
8. History of chronic obstructive pulmonary disease or cor pulmonale, or substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression.
9. Active positive Hepatitis B, C and/or HIV serologies (see *Appendix B*).

10. Positive urine drug screening test.
11. Use of chronic prescription medications during the period 0 to 30 days; or over-the counter medications (e.g. antihistamines, topical corticosteroids) and short term (<30 days) prescription medications during the period 0-3 days before a study session (vitamin, herbal supplements and birth control medications not included).
12. Currently taking daily anticoagulants (warfarin, heparin, rivaroxaban, dabigatran, etc…) within the past month prior to entry into the study.
13. Have Crohn's disease.
14. History of blood dyscrasia.
15. Donation or loss of greater than one pint of blood within 60 days of entry to the study.
16. Any prior adverse reaction or hypersensitivity to metronidazole, parabens, other inactive ingredients in the gels or cream or to medical tape products.
17. 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.
18. Consumption (food or drink) of alcohol within 48 hours prior to dose administration.
19. 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.
20. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application site (upper arms), sunburn, raised moles and scars, open sores at application site (upper arms), scar tissue, tattoo, or coloration that would interfere with placement of metronidazole products, skin assessment, or reactions to metronidazole.

5 PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

5.1 Analyses

Metronidazole concentrations will be measured in serum samples collected from each subject. Blood samples (approximately 5 mL (1 tsp)) will be collected during each study session within -60 min prior to gel or cream application and then at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 23 h, 24 h and 25 h post-application. Non compartmental analyses (NCA) will be conducted to estimate the PK parameters such as: maximum serum concentration (C_{max}) and AUC of the serum concentration–time determined by the linear trapezoidal method. All NCA analyses will be conducted using Phoenix® WinNonlin® 6.4 (Pharsight, a Certara Company, CA).

5.2 Final Analysis Plan

The objective of this study is to determine PK parameters (C_{max}, AUC) of metronidazole in healthy adults after using metronidazole 0.75% gels or cream.

Student's t-test or Analysis of variance (ANOVA) followed by post-hoc Bonferroni test will be used, where appropriate, for comparing the differences in the means of the PK parameters and significant differences will be declared at $p<0.05$.

If metronidazole 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.