# Determination of Serum Rivastigmine Levels after Using Rivastigmine Transdermal Delivery Systems with and without Standardized Heat Application in Healthy Human Volunteers

**Short title:** Effect of Heat on Rivastigmine TDS Products

UMB IRB #: HP-00076010

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**Sponsor:**

Food and Drug Administration
Office of Generic Drugs

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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:** | Determination of Serum Rivastigmine Levels after Using Rivastigmine Transdermal Delivery Systems with and without Standardized Heat Application in Healthy Human Volunteers |
| **Population:** | Healthy adults age 18 - 45 years |
| **Number of Sites:** | Single site: University of Maryland School of Medicine (GCRC) |
| **Study Duration:** | Approximately up to 1 year |
| **Subject Participation Duration:** | Approximately 10 weeks including the screening period |
| **Description of Study Product:** | Rivastigmine TDS (Exelon®, 4.6 mg/24 h), Novartis Pharmaceutical Corporation; Rivastigmine TDS (generic, 4.6 mg/24 h), Alvogen, Inc |
| **Objective:** | The aim of the present study is to generate human pharmacokinetic (PK) data in healthy subjects for the purpose of determining heat effect on Exelon® (RLD TDS) and rivastigmine (generic TDS).<br><br>The pharmacokinetic data obtained in this study will be used in combination with in vitro data collected to develop an in vitro-in vivo correlation (IVIVC). |
| **Description of Study Design:** | The study will be an open-label, crossover study (n=12 healthy subjects) over ~10 weeks includes four study sessions with up to a 45 day screening period with one week washout period between study sessions.<br><br>The study contains four study sessions:<br><br>• **Study Session 1:** Exelon® TDS containing 9 mg (4.6 mg/24 h) of rivastigmine base to be worn for ~9 h.<br><br>• **Study Session 2:** Rivastigmine generic TDS containing 6.9 mg (4.6 mg/24 h) of rivastigmine base to be worn for ~9 h.<br><br>• **Study Session 3:** Exelon® TDS containing 9 mg (4.6 mg/24 h) of rivastigmine base to be worn for ~9 h. The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30 minutes at 5 h after application of the TDS. |

**Study Session 4:** Rivastigmine generic TDS containing 6.9 mg (4.6 mg/24 h) of rivastigmine base to be worn for ~9 h. The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30 minutes at 5 h after application of the TDS.

*A) Pharmacokinetics (PK)*

Each subject will be his/her own control (pre-dose blood sample) 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 TDS application. Blood samples (approximately 4 mL each) will be drawn in BD vacutainer tubes. Blood samples will be obtained as follows:

- Within 60 min pre-application and then up to ~12 h after TDS application.

*B) Residual Drug Analysis of Rivastigmine TDS*

In conjunction with the above described study, residual drug analysis will also be conducted for the previously worn Exelon® and rivastigmine generic TDS from Study Session 1-4.

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

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

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

- All items coming into contact with the TDS during removal from the subject will be stored in a separate labeled sealable pouch until analyzed for drug content.

# 1 KEY ROLES

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# 2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background Information

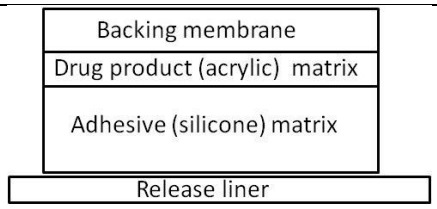
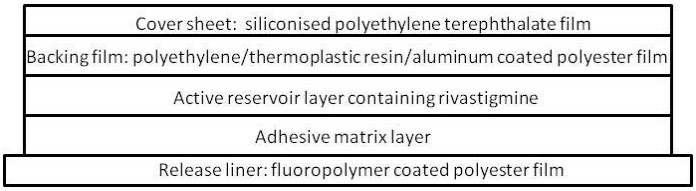
There are numerous transdermal delivery systems (TDS) that are currently available in the United States, the first of which was approved by the Food and Drug Administration (FDA) in 1979 [1]. TDS are very attractive, convenient and easy to use systems and are available in various forms including TDSs (matrix or reservoir), sprays, gels, and ointments. Drug permeation from these TDS varies significantly and is dependent on a number of factors including system design, physicochemical properties of the drug, excipients, occlusion, sweat, skin condition, skin type and temperature. Investigating the influence of these factors on drug permeation from reference products that are often available in different forms is important to ensure that one formulation is not less safe than other formulations. In this proposal we will focus on investigating the influence of heat on drug permeation from rivastigmine RLD and generic TDS. Systemic absorption of drugs is dependent on cutaneous blood flow. Application of, or exposure to heat, allows gradual increase in cutaneous blood flow and an increase in the absorption rate and hence can increase drug permeation from TDSs. Indeed, exposure to heat has been demonstrated to increase drug permeation from TDSs, which led to increased serum concentrations of numerous drugs (e.g., fentanyl and nicotine) and raised a number of safety concerns [2-7]. As a result, almost all TDSs that are currently available have warnings against heat exposure.

## 2.2 Rationale

The goal of this study is to conduct in vivo studies to compare the influence of heat on rivastigmine drug permeation from FDA approved products; Exelon® TDS versus rivastigmine generic TDS. While there is data in the literature for heat effect on different active pharmaceutical ingredients (APIs), specifically RLD products, from exposure to external heating sources (heating pads, sauna, hot showers, exercising), there is no head-to-head comparisons for heat effect on RLD versus generic during application. Therefore, to help ensure that TDS are safe for patients, an in vitro setup is being developed to characterize the heat effect for these systems by correlating the in vivo data with in vitro data using the IVPT model with excised human skin. This necessitates that a small number of human subject heat effect studies are performed under controlled and monitored conditions with selected products, to serve as an in vivo reference for parallel IVPT heat effect studies. The rivastigmine heat effect studies described in this protocol are the final set in this series of studies. The intent of this research is to establish an IVIVC for the IVPT model in the specific context of heat effect studies, so that IVPT studies can be utilized to

evaluate whether all future generic products are similar in quality to the RLD in terms of heat effect. In addition, the residual drug content of the used rivastigmine TDSs will be analyzed for the purpose of estimating the amount of drug absorbed.

**Rivastigmine Products**

| Properties | Exelon TDS | Alvogen TDS |
|---|---|---|
| Excipients | Acrylic copolymer, poly(butylmethacrylate, methyl-methacrylate), silicone adhesive applied to a flexible polymer backing film, silicone oil and vitamin E | Colloidal silicon dioxide, light mineral oil, polyisobutylene adhesive, acrylate-vinylacetate pressure sensitive adhesive, aluminum coated polyester backing |
| Drug load | 9 mg | 6.9 mg |
| Delivery rate | 4.6 mg/24 h (0.19 mg/h) | 4.6 mg/24 h (0.19 mg/h) |
| Size | 5 $cm^2$ | 4.6 $cm^2$ |
| Manufacturer | LTS Lohmann Therapie-Systeme AG | Alvogen, Inc |
| Distributor | Novartis Pharmaceuticals Corp. | Alvogen, Inc |
| |  |  |

# 3 OBJECTIVES

## 3.1 Study Objectives

The present study aims to:

1) Determine serum rivastigmine concentrations after using Exelon® (matrix type TDS, Novartis Pharmaceuticals Corporation) and rivastigmine generic (matrix type TDS, Alvogen, Inc.) with and without standardized heat application in healthy adult subjects.

2) Determine residual drug content of TDSs for the purpose of estimating amount of drug absorbed.

3) Generate human PK data for the purpose of establishing an IVIVC model by collecting data following the application of rivastigmine products: Exelon® and rivastigmine generic TDS.

## 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 rivastigmine and area under the curve (AUC) attained with and without heating for Exelon® TDS and rivastigmine generic TDS. In addition, we will determine residual drug content from worn TDSs to estimate total amount of absorbed rivastigmine.

# 4 STUDY ENROLLMENT

## 4.1 Subject Inclusion Criteria

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

1. Men or non-pregnant, non-lactating 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, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, TDSs or electronic cigarettes) over the previous two months and are not currently 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 or to participate in an investigational drug study for at least one 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. Subjects deemed to be healthy as judged by the MAI and determined by medical history, physical examination and medication history.

8. Negative urine drug screening test (cannabinoids, amphetamines, barbiturates, benzodiazepine, cocaine, methadone, opiates, PCP).

9. Have normal screening laboratories for white blood cells (WBC), hemoglobin (Hgb), platelets, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT) and aspartate aminotransferase (AST).

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

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

12. Agree not to donate blood to a blood bank throughout participation in the study and for at least three months after the last procedure day.
13. 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).
14. 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

## 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 any study session.
2. Smokers/tobacco users (current use or use over the previous two months of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, TDS 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. Positive urine drug screening test.
7. Use of chronic prescription medications during the period 0 to 30 days; or over-the-counter medications (e.g. cholinomimetic drugs [used to treat diseases like acid reflux in children, glaucoma, dry mouth associated with Sjögren's Syndrome], anticholinergics [used to treat diseases like asthma, incontinence, gastrointestinal cramps, and muscular spasms], 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)].

8. Donation or loss of greater than one pint of blood within 60 days of entry to the study.

9. Any prior adverse reaction or hypersensitivity to rivastigmine, other carbamate derivatives, other ingredients in the TDS tested, to medical tape products or other skin TDSs.

10. Subject has problems with urinary retention, gastric retention or gastrointestinal obstruction.

11. Subject has continuous spasms, muscle contractions, motor restlessness, rigidity, slowness of movement, tremors or irregular jerky movements.

12. Subject has ulcers or gastrointestinal bleeding.

13. Subject has history of asthma or blocked airflow making it hard to breathe (COPD).

14. Received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within one month before enrollment in this study or expects to receive an experimental agent during the study.

15. 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.

16. 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., psoriasis, atopic dermatitis).

17. History of diabetes.

18. Hereditary skin disorders or any skin inflammatory conditions as reported by the subject or evident to the MAI.

19. 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.

20. At application site (upper arms), subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hairand refuses to clip hair , sunburn, raised moles and scars, open sores, scar tissue, tattoo or coloration that would interfere with placement of products, skin assessment or reactions to rivastigmine.

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

# 5 PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

## 5.1 Analyses

Rivastigmine concentrations will be measured in serum samples collected from each subject. Blood samples (approximately 4 mL or 5 mL (~1 tsp)) will be collected within 60 min of pre-application and then at 2 h, 3 h, 4 h, 5 h, 5 h 15 min, 5 h 30 min, 5 h 45 min, 6 h, 6 h 15 min, 6 h 30 min, 7 h, 7 h 30 min, 8 h, 8 h 30 min, 9 h, 9 h 15 min, 9 h 30 min, 10 h, 11 h and 12 h post-TDS application.

Non compartmental analyses (NCA) will be conducted to estimate the PK parameters such as: maximum serum concentration ($C_{max}$), 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 (TDS);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).

## 5.2 Sample Size Considerations

To calculate the sample size required to achieve an 80% power, we considered a parameter estimate (area under the curve (AUC)) with a maximum error within 25% of the reported value to be acceptable. The sample size calculation used was reported by Panetta et al. and is as follows [9]:

$$n = \frac{(Z_\alpha + Z_\beta)^2 * \varsigma^2}{\varepsilon^2}$$

where n represents the sample size required, $Z_\alpha$ represents the z score for the type 1 error, $Z_\beta$ represents the z score for the type 2 error, ς represents the standard deviation of the parameter and ε represents the predicted error of the parameter estimate. The type 1 error was fixed to 5% and the type 2 error was fixed to 20%.

For Exelon®, assuming a mean ± SD $AUC_{24h}$ of 166 ± 50 ng*h/mL (30% CV), the sample size calculations using the above formula indicated that n=12 subjects would provide a power of 82% for a predicted error of 25% on the AUC [8].

## 5.3 Final Analysis Plan

An objective of this study is to investigate the influence of heat application on the PK parameters of rivastigmine after using a RLD or generic TDS. The primary PK parameters

to be compared are 1) $C_{max}$, before and after heat application; 2) AUC before and after heat application consistent with similar PK studies[6,7]. Determine PK parameters ($C_{max}$, AUC) of rivastigmine in healthy adults after using Exelon® and rivastigmine generic TDS for the purpose of IVIVC by collecting data. Complimentary in vitro data will be collected using human skin.

IVIVC will be conducted comparing PK parameters and profiles to predicted PK parameters and profiles using IVPT 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:

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

$C_{ss}$=steady state serum concentration; $J_{ss}$=steady state flux; A=area; *CL*=clearance

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

**Intra-procedure comparisons:**

For Study Session 1-4:

- $C_{max}$ will be compared among the following time periods: 0-5 h, 5 h-6 h 30 min, 6 h 30 min-9 h and 9-12 h post TDS application
- AUC: will be compared among the following time periods: 0-5 h, 5 h-6 h 30 min, 6 h 30 min-9 h and 9-12 h post TDS application

**Inter-procedure comparisons:**

For Study Session 1-4: Both $C_{max}$ and AUC will be compared among procedure groups for the following time periods: 5 h -6 h 30 min.