A Phase 1, Open-Label, 3-Period, Randomized, Crossover Pharmacokinetic Study to Evaluate the Steady-State Pharmacokinetics of 5 mg and 10 mg Corplex™ Donepezil Transdermal Delivery Systems Compared to 10 mg Oral Administration of Aricept® in Healthy Volunteers

Protocol No: CL-P-20003

Original Protocol dated: October 2, 2020
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Sponsor Approval / Signature Page

Protocol Number	CL-P-20003
Protocol Version Date	Amendment #1 October 26, 2020
Investigational Product	Corplex™ Donepezil Transdermal Delivery System (TDS) is a matrix type transdermal patch manufactured for a 7-day application.
IND Number	129778
Study Phase	Phase 1
Sponsor	Corium, Inc. 4558 50th St SE Grand Rapids, MI 49512 USA Tel: 616-656-4563 x226
Principal Investigator	[redacted]
Medical Monitor	[redacted]

[redacted]

Charles Oh, MD Date
Chief Medical Officer, Corium, Inc.

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Principal Investigator's Statement / Signature

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct this study as outlined in the protocol, Master Clinical Services Agreement, Statement of Work, and any change orders/amendments to these documents.

I understand the study protocol and will conduct the study according to the procedures therein and according to the principles of Good Clinical Practice and all applicable federal and local regulations.

I will ensure that all individuals assisting with the study are adequately trained and informed about the protocol, investigational product(s), procedures and their study related duties and functions.

I agree not to deviate from the protocol without prior agreement from the Sponsor except to eliminate an immediate safety hazard to the study subjects.

I further agree that the Sponsor, Sponsor designees and federal agencies, shall have access to all source documents and records associated with the study for review and monitoring of the investigational trial.

[redacted]

[redacted]
Signature Principal Investigator

[redacted]
Date

[redacted]
Name of Investigational Site

[redacted]
Address of Investigational Site

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADL	Activity of Daily Living
ALT	Alanine transaminase
AST	Aspartate aminotransferase, Aspartate transaminase
AUC	Area under the plasma concentration-time curve
β-hCG	Beta human chorionic gonadotropin
BLQ	Below the limit of quantification
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate (eGFR)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
C_{tau}	Plasma concentration at the end of a dosing interval at steady state
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical Research Unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FLUCP	Percent peak-to-trough fluctuation
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
LSGM	Least squares geometric mean
MedDRA	Medical Dictionary of Regulatory Activities
OTC	Over the Counter
PD	Pharmacodynamic
PK	Pharmacokinetic

PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q1	25th Percentile (1st Quartile)
Q3	75th Percentile (3rd Quartile)
QTcF	Time between the start of the Q wave and the end of the T wave (QT interval) in the heart's electrical cycle, corrected for heart rate with Fridericias's formula
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOE	Schedule of Events
SS	Steady State
TDS	Transdermal Delivery System
TEAE	Treatment-Emergent Adverse Event
T_{lag}	Lag time: time prior to the first measurable (non-zero) concentration
T_{max}	Time to achieve the maximum observed plasma concentration
ULN	Upper Limit of Normal

PROTOCOL SYNOPSIS

TITLE	A Phase 1, Open-Label, 3-Period, Randomized, Crossover Pharmacokinetic Study to Evaluate the Steady-State Pharmacokinetics of 5 mg and 10 mg Corplex™ Donepezil Transdermal Delivery Systems Compared to 10 mg Oral Administration of Aricept® in Healthy Volunteers
SPONSOR	Corium, Inc.
PROTOCOL NUMBER	CL-P-20003
INVESTIGATIONAL PRODUCT	Corplex™ Donepezil Transdermal Delivery System (TDS) is a matrix type transdermal patch manufactured for a 7-day application.
NAME OF ACTIVE INGREDIENT	Donepezil
ROUTE	Oral/Transdermal (TDS)
NUMBER OF SITES	1
STUDY DESIGN	This is a Phase 1, open-label, randomized, 3-period, 3-treament, crossover pharmacokinetic study to evaluate the steady-state pharmacokinetics of 5 mg and 10 mg Corplex™ Donepezil TDS manufactured with the commercial process compared to 10 mg oral administration of Aricept® in healthy volunteers. The study will consist of a Screening Period, a Treatment Phase with 3 treatment periods and a Follow-Up Visit, as follows: • Screening Period: Subjects will undergo a Screening Period up to 28 days prior to entering the Treatment Phase. • Treatment Phase: Eligible subjects will participate in 3 treatment periods each consisting of 36 days, without a washout between treatments. o **Treatment A**: 5 mg/day Donepezil Transdermal Delivery System (TDS) for 5 consecutive weeks (7-day wear for each of the 5 patches). In Period 1, all enrolled subjects will receive Treatment A. The last (5^{th}) patch will be removed on the morning of Day 36 (168 hours after the last patch application). No study drug will be administered on Day 36. During Period 1, the 5 mg/day Donepezil TDS as the first treatment of the study allows subjects to get accustomed to the potential cholinergic effects (5 mg/day for 1 week is the recommended starting dose before titrating up, to 10 mg/day). In this study, the 5 mg/day Donepezil TDS is administered for

	5 weeks to reach steady state in order to measure the steady state pharmacokinetics in Week 5 to be compared with those after oral Aricept®. During Treatment Periods 2 and 3, the subjects will be randomized to receive either sequences of Treatments B-C or Treatments C-B. Subjects will receive the following treatments according to the randomization schedule. o **Treatment B**: 10 mg/day Donepezil TDS applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks o **Treatment C**: 10 mg Aricept® donepezil tablet administered QD for 5 weeks (within ±1 hour of dosing time on Day 1). Randomization to the 2 treatment sequences will be stratified by gender. For all oral doses and TDS applications, subjects will receive a light meal 30 minutes prior to dosing. Standard meals will be provided at appropriate times thereafter. Blood samples for pharmacokinetics and safety assessments will be collected during the Treatment Phase. See Treatment Phase Schematic (Section 2). In each period wherein the treatment consists of a patch, the subjects will wear a total of 5 patches (1 per week) for a total of 35 days (5 weeks). The last (5^{th}) patch in the period will be removed after the morning blood draw on Day 36 (168-hour time point after the last patch in the period). No treatment will be administered on Day 36 of the period; additional post-wear PK blood samples will be collected on Day 36 after any patch treatment. In each period (Period 2 or 3) wherein the treatment consists of oral Aricept®, the subjects will receive an oral dose daily for a total of 35 days (5 weeks). The last oral dose in the period will be administered on the morning of Day 35. No treatment will be administered on Day 36 of the period; a PK blood sample will be collected in the morning of Day 36 at 24 hours after the last oral dose. In Period 1, all subjects will wear patches (Treatment A). In Periods 2 and 3, subjects will either wear patches (Treatment B) or receive once-per-day oral Aricept® (Treatment C). o The treatment in Period 2 will start on the morning of Study Day 37 after the pre-dose blood draw for

	Period 2 is collected. No treatment will be administered on Study Day 72. For the patch treatment in Period 2, the patch will be removed on Study Day 72 after the 168-hour blood sample collection. o The treatment in Period 3 will start on the morning of Study Day 73 after the pre-dose blood draw for Period 3 is collected. No treatment will be administered on Study Day 108. For the patch treatment in Period 3, the patch will be removed on Study Day 108 after the 168-hour blood sample collection. • **Follow-Up Visit**: 5 ±2 days after the day of the last oral drug administration or last TDS removal during the Treatment Phase, subjects will enter a Follow-Up Visit to evaluate safety parameters. **There will be no washout phase between treatment periods (with the exception of Day 36 within each period to collect post-treatment PK blood samples).**
PRIMARY OBJECTIVE	To evaluate the bioequivalence of steady-state donepezil plasma exposure following once-weekly treatments with 10 mg/day Corplex™ Donepezil TDS compared to once-daily oral administration of 10 mg Aricept®.
SECONDARY OBJECTIVES	• To evaluate the bioequivalence of steady-state donepezil plasma exposure (after dose-normalization) following once-weekly treatments with 5 mg/day Corplex™ Donepezil TDS compared to once-daily oral administration of 10 mg Aricept®. • To evaluate the adhesion to the skin during the wear period of each once-weekly 5 mg/day and 10 mg/day Corplex™ Donepezil TDS application.
SAFETY OBJECTIVE	To evaluate the safety and tolerability (including local skin tolerability, which consists of Dermal Response and Other Effects) of once-weekly Corplex™ Donepezil TDS.
NUMBER OF SUBJECTS	An appropriate number of subjects will enter the Screening Period to enroll approximately 60 subjects to complete with 48 subjects during the Treatment Phase.
SUBJECT SELECTION CRITERIA	**Inclusion Criteria** 1. Healthy males and females. 2. Subject must be a male or non-pregnant, non-breastfeeding female. 3. Subject must be between 18 and 55 years of age (inclusive) at Screening. 4. Subject's Body Mass Index (BMI) must be between 18 and 32 kg/m^2 (inclusive) and subject must weigh

	between 60 and 100 kg (inclusive) at Screening. 5. Subject must be continuous non-smokers and agree not to smoke during confinement from the time of screening and throughout the study. 6. Subject must have a Fitzpatrick skin type of I, II or III or have skin colorimeter scores equivalent to the allowed Fitzpatrick skin type. 7. Female subjects must agree to use one of the following forms of birth control from screening until 14 days after the End-of-Study Visit, unless a different timeframe is listed below: a) Vasectomized partner (at least 6 months prior to Screening). b) Post-menopausal (at least 2 years prior to Screening). c) Surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to Screening. d) Non-surgical sterilization (e.g., Essure® procedure) at least 3 months prior to Screening. e) Double barrier (diaphragm with spermicide; condoms with spermicide) f) Intrauterine device (IUD) g) Total abstinence (must agree to use a double barrier method if they become sexually active between Screening and 14 days after the End-of-Study Visit). h) Implanted or intrauterine hormonal contraceptives in use for at least 3 consecutive months prior to Screening. i) Oral, patch, or injected contraceptives, or vaginal hormonal device (i.e., NuvaRing®), in use for at least 3 consecutive months prior to Screening. 8. Subject must be able to speak, read and understand English or Spanish. 9. Subject must voluntarily consent to participate in this study and provide their written informed consent prior to start of any study-specific procedures. 10. Subject is willing and able to remain in the study unit for the entire duration of each confinement period and return for the Follow-Up Visit. **Exclusion Criteria** 1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal,

	hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results. 2. More specifically, subjects with a history of serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other cardiac problems. 3. More specifically, at the discretion of the Investigator, subjects with preexisting hypertension, heart failure, myocardial infarction, or ventricular arrhythmia/prior EEG abnormalities in absence of seizure. 4. At the discretion of the Investigator, a clinically significant abnormal finding in the physical examination, vital signs, medical history (including a family history of sudden death/ventricular arrhythmia), electrocardiogram (ECG), or clinical laboratory results at Screening. 5. After resting seated for at least 3 minutes, subjects should be excluded from the study with the following vital signs at Screening: a) a confirmed systolic blood pressure outside the range of 90-145 mmHg, or b) a confirmed diastolic blood pressure outside the range of 50-90 mmHg, or c) a confirmed resting heart rate outside the range of 40-100 beats per minute. 6. Has an isolated alanine aminotransferase (ALT) ≥1.5x the Upper Limit of Normal (ULN) or aspartate aminotransferase (AST) ≥1.5x the ULN at Screening; or both ALT and AST exceeding the ULN. 7. Estimated creatinine clearance at screening <70 mL/min/1.73 m^2 using the CKD-EPI equation calculator (Levey 2009). 8. Prolonged corrected QT interval by Fridericia's formula (QTcF) on screening electrocardiogram (ECG) (≥450 ms for both females and males). 9. History of significant multiple and/or severe allergies (e.g., latex allergy, band aids, adhesive dressing, or medical grade adhesive tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs. 10. Major surgery that required general anesthesia within 90 days prior to Screening. 11. History or presence of hypersensitivity or

	idiosyncratic reaction to the study drugs or related compounds (including piperidine derivatives and other cholinesterase inhibitors). 12. At the discretion of the Investigator, on a significantly abnormal diet during the 4 weeks preceding Day -1. 13. History or presence of excessive hairy skin on application sites as deemed by the Investigator to potentially interfere with patch adhesion or drug absorption. 14. History or presence of significant skin damage, diffuse skin diseases (e.g., diffuse psoriasis or eczema), scars (flat scars, birth marks, moles, and stretch marks that do not affect skin surface are allowed), tattoos on the application sites or other skin disturbances (including sunburns, excessive tanning, and stretch marks) as deemed by the Investigator to potentially interfere with drug absorption or skin tolerability assessments 15. Use of donepezil hydrochloride or related drugs within 60 days prior to the first study drug administration (oral administration or TDS application, as appropriate). 16. Has donated ≥500 mL blood within 30 days or donated ≥500 mL plasma within 14 days prior to Day -1. 17. Inadequate peripheral venous access that would interfere with obtaining blood samples. 18. Has participated in another clinical trial (randomized subjects only) within 30 days prior to Day -1. 19. Has used any over the counter (OTC) medication, including vitamins, herbal products, and dietary supplements within 14 days prior to Day -1. 20. Has used any prescription medication, except hormonal contraceptive or hormonal replacement therapy, within 14 days prior to Day -1. 21. Has a history of substance abuse or treatment (including alcohol) within 1 year prior to Screening. 22. Is a female with a positive pregnancy test. 23. Has a positive urine screen for drugs of abuse at Screening or Day -1. 24. Has a positive urine screen for alcohol on Screening or Day -1. 25. Has a positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody at Screening or has been previously treated for hepatitis B, hepatitis C, or HIV infection.

	26. Has an active COVID-19 test at Screening or Day -1. 27. Has clinically significant gastrointestinal problems, including narrowing of the gastrointestinal tract, that may interfere with the gastrointestinal absorption of study drug. 28. History of eating disorders within 3 months prior to Day -1. 29. Has a history of unstable psychiatric illness requiring medications or hospitalization within 12 months prior to Day -1, or exhibits marked anxiety, tension, or agitation. 30. Specifically, diagnosis of comorbid bipolar disorder/comorbid depressive symptoms. 31. Has a history of unexplained syncope. 32. Subject has any history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at Screening or Day -1. 33. Has smoked or used tobacco products within 6 months prior to Day -1 or is currently using nicotine products; is unable to abstain from the use of any nicotine-containing products (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges). 34. Subject is an employee or relative of any employee working for the CRO or Sponsor.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	The study treatments are as follows: **Treatment A (Test):** 5 mg/day Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each). All subjects will receive Treatment A in Period 1. The patch will be removed on the morning of Day 36. At the start of Period 2, subjects will be randomized to one of the following treatments in Period 2. Subjects will receive the alternate treatment in Period 3. Randomization to the 2 treatment sequences will be stratified gender. **Treatment B (Test):** 10 mg/day Corplex™ Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each). **Treatment C (Reference):** 10 mg Aricept® donepezil (1 x 10 mg/day tablet) administered QD for 35 consecutive days

	(within ±1 hour of dosing time on Day 1). This is the Reference Listed Drug (RLD). See Treatment Phase Schematic (Section 2). In each period wherein the treatment consists of a patch, the subjects will wear a total of 5 patches for a total of 35 days (5 weeks). The last (5^{th}) patch in the period will be removed after the morning blood draw on Day 36 (168-hour time point). No treatment will be administered on Day 36 of the period; additional post-wear PK blood samples will be collected on Day 36 after any patch treatment. In each period wherein the treatment consists of oral Aricept®, the subjects will receive an oral dose daily for a total of 35 days (5 weeks). The last oral dose in the period will be administered on the morning of Day 35. No treatment will be administered on Day 36 of the period; a PK blood sample will be collected in the morning of Day 36 at 24 hours after the last oral dose. In Period 1, all subjects will wear patches (Treatment A). In Periods 2 and 3, subjects will either wear patches (Treatment B) or receive once-per-day oral Aricept® (Treatment C). o The treatment in Period 2 will start on the morning of Study Day 37 after the pre-dose blood draw for Period 2 is collected. No treatment will be administered on Study Day 72. For the patch treatment in Period 2, the patch will be removed on Study Day 72 after the 168-hour blood sample collection. o The treatment in Period 3 will start on the morning of Study Day 73 after the pre-dose blood draw for Period 3 is collected. No treatment will be administered on Study Day 108. For the patch treatment in Period 3, the patch will be removed on Study Day 108 after the 168-hour blood sample collection. **TDS Administration (Treatments A and B):** • The pharmacy at the CRU will remove the TDS from refrigerated storage (2-8ºC) and place at room temperature storage (20-25ºC) on the day before application, no more than 24 hours prior to application. • The pharmacy at the CRU will prepare the Corplex™ Donepezil TDS for each subject (per the randomization and stratification scheme). Each TDS treatment will be applied to intact dry skin only on the

	subject's back weekly for 5 consecutive weeks. The most ideal naïve location on the back (back area that avoids the bra area and is slightly above the waistline is preferred) should be reserved for the last 5th patch of the treatment sequence. If this is not possible Sponsor approval should be obtained and documented to apply the TDS to a previously used site. • It is recommended that the TDS is applied to the subject within 120 minutes of opening/removing from the packaging. • Subjects will be instructed to shower from 1 to 2 hours prior to each TDS application. No more than 1 shower a day is permitted and if showers are not taken, the following will be performed within 1 to 2 hours prior to each TDS application: the application area will be washed with room temperature water using a wet washcloth. The application site will be patted dry and will be checked for irritancy. • The application area will be identified with a template overlay. The TDS will be placed at the designated application site and firm pressure will be applied immediately over the TDS for approximately 20 seconds using the palm of the hand on each TDS to ensure adhesion. A new TDS should not be applied to an area of skin where a TDS was just removed. The area selected should not be oily, damaged, or irritated and should not be exposed to sunlight. • No taping of the transdermal delivery systems will be allowed. • The exact clock time of TDS application and removal will be recorded for the start and end of TDS application. During each TDS treatment, the next TDS will be applied as soon as the previous TDS was removed. The change in TDSs should be performed within 15 minutes. **<u>Oral Drug Administration (Treatment C)</u>:** Study drug will be given orally and be administered with approximately 240 mL of water. Subjects will be instructed not to crush, split, or chew the study drug tablets.
EVALUATION CRITERIA	The evaluation criteria of the study are based on pharmacokinetic assessments, TDS adhesion assessments, and safety evaluations. Pharmacokinetic Sampling (Days listed are days within each period. See Treatment Phase Schematic, Section 2):

	The blood PK samples will be collected at the nominal time points listed below ±5 minutes for the first 24 hours and 10 minutes thereafter. **Treatments A and B (patch applications):** The following blood PK samples will be collected in 2 mL EDTA K2 lavender top tubes. • Week 1 (Days 1 to 7): Pre-TDS #1 application (Day 1), and at 2, 6, 12, 24, 48, 72, 96, 120, and 144 h after TDS #1 application. • Week 2 (Days 8 to 14): Pre-TDS #2 application (Day 8 at 168 h after TDS #1 application), and at 24, 48, 72, 96, 120, and 144 h after TDS #2 application. • Week 3 (Day 15 to 21): Pre-TDS #3 application (Day 15 at 168 h after TDS #2 application). • Week 4 (Day 22 to 28): Pre-TDS #4 application (Day 22 at 168 h after TDS #3 application). The following blood PK samples will be collected in 4 mL EDTA K2 lavender top tubes. • Week 5 (Day 29 to 35): Pre-TDS #5 application (Day 29 at 168 h after TDS #4 application), and at 3, 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156 h after TDS #5 application • Week 6 (Day 36): Pre-TDS #5 removal (Day 36 at 168 h after TDS #5 application), and at 2, 6, 8, 10, and 12 h after TDS #5 removal **Treatment C (oral donepezil):** The following blood PK samples will be collected in 2 mL EDTA K2 lavender top tubes. • Week 1, Day 1: Pre-Dose, and at 1, 2, 3, 4, 6, 8, 12 and 24 h after oral administration (before Day 2 oral administration) • Week 2: Day 8 Pre-Dose • Week 3: Day 15 Pre-Dose • Week 4: Day 22 Pre-Dose The following blood PK samples will be collected in 4 mL EDTA K2 lavender top tubes • Week 5: Day 29 Pre-Dose • Week 5: Day 35 Pre-Dose, and 1, 2, 3, 4, 6, 8, 12 and 24 h after oral administration (the 24-h sample will be collected on Day 36) **Adhesion:** Trained observers will determine the adhesion of each TDS as the percentage of the total surface area that is adhered to the skin.

	Safety: The Investigator will assess safety using the following parameters: physical examinations, vital sign assessments, clinical laboratory evaluations, C-SSRS evaluations, electrocardiograms, and skin tolerability assessments (Dermal Response and Other Effects). Subjects will be monitored for any adverse events (AEs) from the time of first drug administration through the Follow-Up Visit.
STUDY PARAMETERS	**Pharmacokinetic** Pharmacokinetic parameters at steady state (Week 5) calculated for plasma concentrations of donepezil and 6-O-desmethyl donepezil (active metabolite) will include $AUC_{0-24,SS}$ (daily AUC), $AUC_{0-168,SS,}$ C_{max}, C_{min}, C_{avg}, C_{tau}, percent peak-to-trough fluctuation (FLUCP). After oral administration, $AUC_{0-24,SS}$ will be calculated and multiplied by 7 to obtain $AUC_{0-168,SS}$. **Safety** Safety will be assessed through 12-lead ECGs, vital sign measurements, clinical laboratory tests, suicidality monitoring (as per the C-SSRS), AEs, and physical examinations. Skin tolerability assessments will be performed for each TDS treatment prior to the TDS application and after removal of the TDS application. **Adhesion** Adhesion assessments of each TDS will be collected every 12 hours during TDS wear as the percentage of the total surface area that is adhered to the skin, assessed in person by trained observers. With each consecutive measurement, observers will record the percentage based upon the actual measurement at each time point with the observer blinded to the previous recorded percentage finding. Tactile pressure to the TDS must not be applied during the adhesion determinations. A grid overlay with boxes will be used to assist with estimating the % adhesion. No taping of the TDS will be allowed. The time of full detachment of any TDS and its 0% adherence will be recorded, and the 0% adhesion will be assigned to all remaining adhesion time points of the current wear period. At each adhesion assessment time point, a photograph will be taken as evidence of the extent of TDS adhesion to the skin (as support of the visual observation of the adhesion percentage but not to be used for automated or photometric analysis).

	Following removal of each TDS, the presence or absence of remaining adhesive residue will be recorded. **Skin Tolerability** Skin Tolerability assessments will be performed prior to the TDS application and after removal of the TDS application during each period. If application site score is other than a 0 prior to TDS application, another site will need to be used. **Residual Donepezil** The used TDSs will be returned to Corium for residual drug analysis (inclusive of any TDS that will be replaced during the study).
STATISTICAL ANALYSES	**Pharmacokinetics** Plasma concentrations and PK parameters of donepezil and 6-O-desmethyl donepezil will be tabulated using summary statistics. To examine the donepezil PK at steady state (Week 5 of 5 x 1-week wear) after 5 and 10 mg/day TDS application compared to oral Aricept®, an analysis of variance (ANOVA) will be performed on the natural logarithms of $AUC_{0\text{-}168,SS}$ and C_{max}. Dose-normalization will be applied as appropriate. Differences between each Test and Reference in the PK parameters will be tested at the 5% level of significance. **Time to Steady State Assessment** Assessment of time to achieve steady-state will be performed by a review of weekly donepezil trough levels (C_{tau}) at time points immediately prior to dosing on Days 15, 22, 29, and 36 in each treatment period. The univariate analysis method described by Chow and Liu for examining when steady-state is attained will be implemented using log-transformed trough plasma concentrations. Modifications to the method for Treatment Periods 2 and 3 will be explained in the Statistical Analysis Plan (SAP), to possibly adjust for the attainment of a new steady state after switching to a new treatment without a washout period after the previous treatment. **Relative Bioavailability** To examine the relative bioavailability at steady state of the 5 and 10 mg/day TDS (Tests) relative to oral donepezil (Reference), plasma donepezil exposure as characterized by $AUC_{0\text{-}168}$ at steady state will be assessed and compared utilizing bioequivalence criteria. Since the intention of the patch is to decrease the peak-to-

	through fluctuations with lower C_{max} after the patch application compared to daily oral Aricept dosing, rather than using the conventional bioequivalence criterion for C_{max}, it is stipulated that mean steady-state donepezil C_{max} after patch administration should remain between the steady-state C_{max} and C_{min} after daily oral Aricept® administration. **Safety** Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities® (MedDRA). The numbers of subjects with AEs, serious AEs (SAEs), and AEs leading to withdrawal from the study will be summarized by Preferred Term and System Organ Class for each treatment. Continuous safety data will be summarized by observed value and by change from baseline at each scheduled assessment. Concomitant medications will be coded using the current version of World Health Organization drug dictionary and will be listed by subject. Columbia-Suicide Severity Rating Scale item responses will be listed and an overall summary of any suicidal ideation and behavior will be presented in tabular format. **Adhesion** TDS adhesion score results (percentage adhesion) for each TDS strength will be summarized separately for Weeks 1 through 5 and across all wear periods (Weeks 1-5 combined) as follows: • Summary statistics (mean, SD, minimum, Q1, median, Q3, maximum) for the mean adhesion score, where the mean adhesion score for each patch is the average of the patch adhesion scores across the entire wear period. • Adhesion score distribution at each adhesion measurement time point post patch application (i.e., 12, 24, …, and 168 hours) • Average adhesion score at each adhesion measurement time point post patch application • Number (%) of patches that are completely detached during the 7-day wear period • Number (%) of patches with adhesion <50% at any adhesion measurement time point during the 7-day wear period • Summary of frequency of time a patch was first observed with adhesion <50% during the 7-day wear period

	• Number (%) of patches with adhesion ≥75% at all adhesion assessment time points during the 7-day wear period To assess whether at least 80% of the TDS applied are at least 75% adhered throughout the 7-day wear period, a one-sided 95% confidence interval will be determined for the probability (p) that a randomly selected TDS maintains at least 75% adhesion throughout the entire wear period. If the 95% lower confidence limit for p is greater than 80%, acceptable TDS adhesion will be concluded. The method for the calculation of the 95% lower confidence limit and the justification of the method will be provided in the SAP. To calculate the mean adhesion score and associated statistics, the lowest adhesion score at each time point after the baseline time point (t_0) will be carried forward to subsequent time points until a lower score is observed. **Patch Detachment:** If a TDS partially or fully detaches from the skin, actions to reapply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., taping) must be avoided throughout the study. TDS detachment must not be inappropriately inhibited (e.g., by the constant pressure applied by a person or an object such as the back of a chair). If a TDS fully detaches from the skin, the TDS must not be reapplied and no fresh TDS will be applied for the remainder of the intended wear period. The time of full detachment of any TDS and its 0% adherence will be recorded, and the 0% adhesion will be assigned to all remaining adhesion time points of the current wear period. **Skin Tolerability Assessments:** Dermal response scores, other effects numerical scores, and the combined skin irritation score (calculated as the sum of the dermal response and other effects scores) will be summarized by post removal time point (0.5, 24, 48, 72 hours post removal). The Dermal Response scale combined with the Other Effects scale is what defines the Local Skin Tolerability Assessment. Whole number scores will be used. When evaluating a dermal response, at least 25% or more of the patch area should demonstrate an observable response. When multiple observable dermal responses are present, each observable response shall represent at least 25% or more of

the patch area. It is recommended when determining the percentage of patch area with an observable response, record each dermal response and determine if each one response represents at least 25% or more of the patch area. Skin irritation will be followed until skin tolerability scores are ≤1. Separate summaries by treatment and by post removal assessment time point will be provided.
If a TDS detaches, the tolerability scores will be collected for the site from which the TDS was removed.

Skin tolerability assessments will be performed prior to the TDS application and after removal of the TDS application during each period using the following scale:

Dermal Response

Skin Appearance	**Score**
No evidence of irritation	0
Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site	7

Other Effects

Observation	**Score (Numerical Equivalent)**
Slightly glazed appearance	A (0)
Markedly glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the TDS site	G (3)
Small petechial erosions and/or scabs	H (3)

Source: FDA Draft Guidance: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs. 2018

	Residual Donepezil Results of the residual donepezil content from the used TDSs will be listed and an overall summary will be presented in a report.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will participate in the study for up to 144 days, including up to 28 days of screening, a Treatment Phase with 3 treatment periods of 36 days each, and a 5 ±2 day Follow-Up Visit. Eligible subjects will stay in the research clinic for 109 days (108 overnight stays) during the Treatment Phase

1. SCHEDULE OF EVENTS

STUDY PROCEDURES	SCREENING Day -28 to Day -2	Treatment Phase: Period 1 Day -1 through Day 36										Period 2: Day 37 through Day 72 Period 3 Day 73 through Day 108								Discharge Day 109 Period 3	Early Term[12]	Follow-Up
		Day -1	Day 1,8, 15, 22, 29	Day 2, 9, 16, 23, 30	Day 3, 10, 17, 24, 31	Day 4, 11, 18, 25, 32	Day 5, 12, 19, 26, 33	Day 6, 13, 20, 27, 34	Day 7, 14, 21, 28, 35	Day 8, 15, 22, & 29	Day 36	Day 37, 44, 51, 58, 65, 73, 80, 87, 94,	Day 38, 45, 52, 59, 66,	Day 39, 46, 53, 60, 67, 75, 82, 89, 96,	Day 40, 47, 54, 61, 68, 76, 83, 90, 97,	Day 41, 48, 55, 62, 69, 77, 84, 91, 98,	Day 42, 49, 56, 63, 70, 78, 85, 92, 99,	Day 43, 50, 57, 64, 71, 79, 86, 93, 100,	Day 72 & 108			
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X	X																				
Demographics	X																					
Skin Type Assessment	X																					
Physical Examination	X																		X	X	X	
Height & BMI	X																					
Weight	X																		X	X		
12-Lead ECG[1]	X	X																	X	X		
Vital Signs[2]	X	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	X	
Hem, Serum Chem, Coag, UA[3]	X	X									X							X		X		
COVID-19 Test[54]	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Pregnancy Test (females only)	X	X									X							X	X	X		
Urine Drug & Alcohol Screen	X	X																				
Serology	X																					
C-SSRS[5]	X	X									X							X		X		
Randomization												X										
Drug Administration[6]			X									X										
PK Sampling[7]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Adhesion Assessments[8]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Skin Tolerability Assessments[9]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Skin Photography[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
TDS Removal[11]										X	X							X				

Adverse Event Monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ConMeds Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: , Chem = Chemistry, Coag = Coagulation, ConMeds = Concomitant medication, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = Electrocardiogram, Hem = Hematology, , PK = Pharmacokinetic, TDS = Transdermal Delivery System, UA = Urinalysis.

1. ECG: A 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF). Vital sign measurements will be obtained after the subject has been seated for at least 3 minutes. Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature.
2. Vital signs will be collected prior to the first dose/application of each treatment period and weekly thereafter. Temperature checks may be permitted daily.
3. Hematology, Serum Chemistry, Coagulation Panel, and Urinalysis: Laboratory safety tests will be obtained at the Screening visit, Day -1, Day 36, Day 72, Day 109, and at the Early Termination visit.
4. COVID-19 Testing: Subjects must have an inactive COVID-19 test at Screening and Day -1. COVID-19 testing will occur weekly while subjects are housed in the clinic. Additional test may be conducted at the discretion of the Principle Investigator in consultation with the Medical Monitor.
5. C-SSRS Columbia-Suicide Severity Rating Scale Assessments will be performed at Screening, Day -1, Day 37, Day 72, Day 109, and the Early Termination visit.
6. Drug Administration:
   In Period 1, all subjects will wear patches (Treatment A). In Periods 2 and 3, subjects will either wear patches (Treatment B) or receive once-per-day oral Aricept (Treatment C). There is a treatment-free day on Day 36 of each period.
   In each period wherein the treatment consists of a patch, the subjects will wear a total of 5 patches for a total of 35 days (5 weeks). The last (5th) patch in the period will be removed after the morning blood draw on Day 36 (168 hour time point after the last patch in the period). No treatment will be administered on Day 36 of the period.
   In each period (Period 2 or 3) wherein the treatment consists of oral Aricept, the subjects will take an oral dose daily for a total of 35 days (5 weeks). The last oral dose in the period will be administered on the morning of Day 35. No treatment will be administered on Day 36 in each period.
   TDS Application:

- The pharmacy at the CRU will remove the TDS from refrigerated storage (2-8ºC) and place at room temperature storage (20-25ºC) on the day before application to the skin, no more than 24 hours prior to application.
- It is recommended that the TDS is applied to the subject within 120 minutes of opening/removing from the packaging.
- Subjects will be instructed to shower from 1 to 2 hours prior to each TDS application. No more than 1 shower a day is permitted and if showers are not taken, the following will be performed within 1 to 2 hours prior to each TDS application, the application area will be washed with room temperature water using a wet washcloth. The application site will be patted dry and will be checked for irritancy.
- The application area will be identified with a template overlay. The TDS will be placed at the designated application site and firm pressure will be applied immediately over the TDS for approximately 20 seconds using the palm of the hand on each TDS to ensure adhesion. A new TDS should not be applied to an area of skin where a TDS was just removed. The area selected should not be oily, damaged, or irritated and should not be exposed to sunlight.
  The exact clock time of TDS application and removal will be recorded for the start and end of TDS application. During each TDS treatment period, the next TDS will be applied as soon as the previous TDS was removed. The change in TDSs should be performed within 15 minutes. No taping of the Transdermal Delivery Systems will be allowed.

7. PK Sampling (Days listed are within each period) The blood PK samples will be collected at the nominal time points listed below ±5 minutes for the first 24 hours and 10 minutes thereafter:

   Treatments A and B (patch applications):

   The following blood PK samples will be collected in 2 mL EDTA K2 lavender top tubes:

   - Week 1 (Days 1 to 7): Pre-TDS #1 application (Day 1), and at 2, 6, 12, 24, 48, 72, 96, 120, and 144 h after TDS #1 application.
   - Week 2 (Days 8 to 14): Pre-TDS #2 application (Day 8 at 168 h after TDS #1 application, prior to removal), and at 24, 48, 72, 96, 120, and 144 h after TDS #2 application.
   - Week 3 (Day 15 to 21): Pre-TDS #3 application (Day 15 at 168 h after TDS #2 application, prior to removal).
   - Week 4 (Day 22 to 28): Pre-TDS #4 application (Day 22 at 168 h after TDS #3 application, prior to removal).

   The following blood PK samples will be collected in 4 mL EDTA K2 lavender top tubes

   - Week 5 (Day 29 to 35): Pre-TDS #5 application (Day 29 at 168 h after TDS #4 application, prior to removal), and at 3, 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156 h after TDS #5 application
   - Week 6 (Day 36): Pre-TDS #5 removal (Day 36 at 168 h after TDS #5 application, prior to removal), and at 2, 6, 8, 10, and 12 h after TDS #5 removal

   Treatment C (oral dosing):

   The following blood PK samples will be collected in 2 mL EDTA K2 lavender top tubes:

   - Week 1, Day 1: Pre-Dose, and at 1, 2, 3, 4, 6, 8, 12 and 24 h after oral administration (before Day 2 oral administration)
   - Week 2: Day 8 Pre-Dose

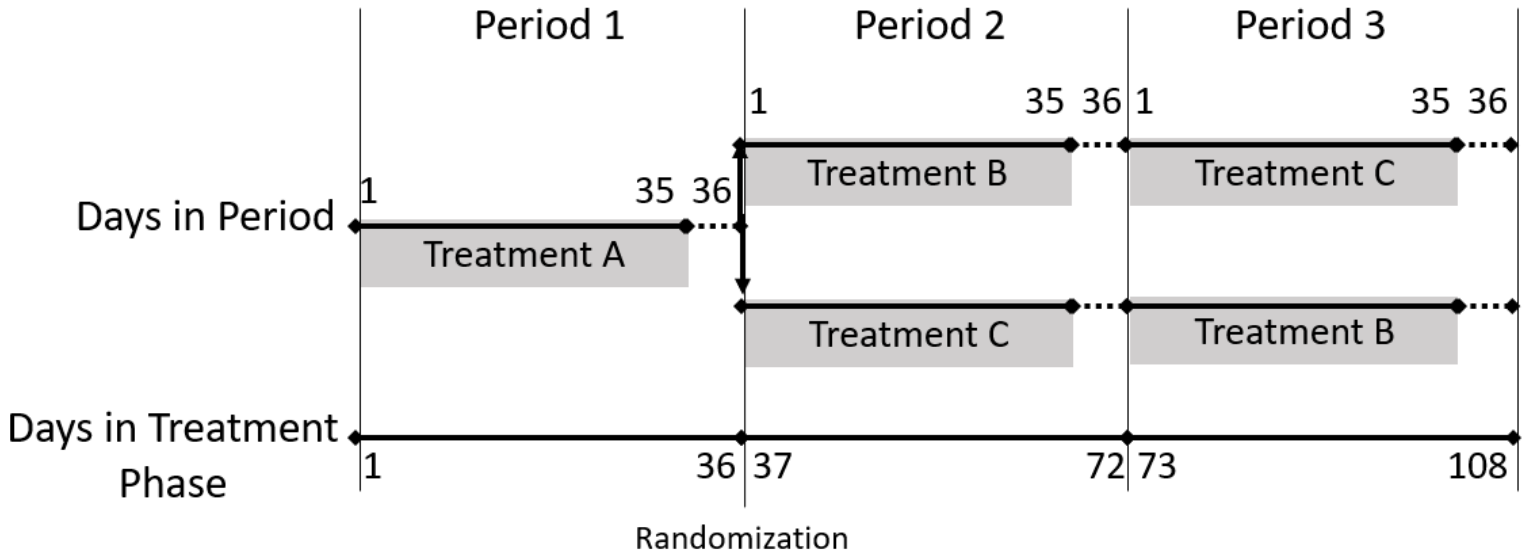
- Week 3: Day 15 Pre-Dose
- Week 4: Day 22 Pre-Dose

The following blood PK samples will be collected in 4 mL EDTA K2 lavender top tubes

- Week 5: Day 29 Pre-Dose
- Week 5: Day 35 Pre-Dose, and 1, 2, 3, 4, 6, 8, 12 and 24 h after oral administration (the 24-h sample will be collected on Day 36).

8. Adhesion Assessments: **Treatment A and B** only - To be performed prior to TDS removal and at specified timepoints. Adhesion assessments will be performed at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168 hour following TDS application. The 168-hour assessment will be conducted prior to the next TDS application. Adhesion assessments will be performed in all periods within ± 1 hour of scheduled assessment.
9. Irritation Assessments: **Treatment A and B** only - The site receiving the TDS should be assessed for skin irritation prior to TDS application (if the score is greater than zero another site must be selected) for Period 1. For TDS applied in during period 2 or 3, the site receiving the TDS should be assessed prior to TDS application (if the score is greater than zero another site must be selected) and the previous week's TDS site should be assessed at 0.5, 24, 48 and 72 hours following TDS removal. If the score is greater than 1 at 72 hours, assessments are to be performed at the following time points until the score returns to $\leq$1: 120 and 168 hours post-removal and then every 3 days. For TDS applied in Week 5, the site receiving the TDS should be assessed prior to TDS application (if the score is greater than zero another site must be selected) and the previous week's TDS site should be assessed at 0.5, 24, 48 and 72 hours following TDS removal.
10. Skin Photography: **Treatment A & B only** - A photograph of the TDS will be taken in conjunction with the adhesion assessments. Adhesion assessments will be performed at baseline and every 12 hours during TDS wear, and when the TDS is removed (including patch removal at or before Early Termination).
11. TDS Removal: **Treatment A and B only** – TDS removal will occur on Day 8, Day 15, Day 22, Day 29, and Day 36 of Period 1 and Days 44, 51, 58, 65, 72, 80, 87, 94, 101, and 108 for Period 2 and 3. Immediately after removal, used TDSs will be collected and returned to the Sponsor. After TDS removal, the presence or absence of adhesive residue on the skin will be recorded. As soon as the TDS has been removed from the skin, the used TDS will be placed adhesive side down, on to a new release liner or folded in half and placed into a foil pouch. The sealed, labeled foil pouch and the corresponding original labeled patch pouch will then be inserted into a plastic bag and stored at approximately -20°C (-4°F) The used TDS will be shipped to the Sponsor, for residual drug determination. Additional instructions regarding application and removal of the TDS are provided in the Pharmacy Manual.
12. Early Termination: Adhesion, tolerability and photos will be performed as needed if early termination occurs when the TDS is still being worn.

TREATMENT PHASE SCHEMATIC



Treatment A: 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period Day 36
Treatment B: 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period Day 36
Treatment C: 10 mg oral Aricept® tablets, QD for 35 days (no dosing on Day 36 of the period)

TDS Application: The first patch in each period with patch treatments (Treatment A or B) will be applied on Treatment Phase Days 1, 37, and 73. For patches #2 to #4, at the end of each week of patch wear (168 h after application), the worn patch will be removed and a new patch will be applied. The 168-h post-dose PK blood samples will be collected before removal of the worn patch.
The last (5^{th}) patch in each period with patch treatments (Treatment A or B) will be removed after 168 hours of the last patch application, after the 168-h PK blood sample collection.
Oral Dosing: In periods with oral Aricept (Treatment C), a single dose will be administered daily on Treatment Phase Days 37-71 (Period 2) and 73-107 (period 3).
Drug-Free Days: There is no study drug administration (neither patch wear nor oral dosing) on Treatment Phase Days 36, 72, and 108.

2. BACKGROUND

2.1. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of unknown etiology, characterized by progressive cognitive decline. Due to the role of cholinergic forebrain projections in memory and learning, several researchers proposed a cholinergic hypothesis to explain at least some of the features of AD. In the cholinergic hypothesis, cholinergic neurons emanating from the basal forebrain (nucleus of Meynert) are selectively lost. A corollary of this hypothesis is that augmentation of available cholinergic input to the forebrain could ameliorate AD symptoms. One method to augment cholinergic input would be to increase the levels of acetylcholine (ACh) in the synaptic cleft by inhibiting its degradation by the enzyme acetylcholinesterase (AChE).

2.2. Donepezil

Donepezil HCl is one of 5 drugs approved for the treatment of AD. Aricept® (donepezil HCl) is approved for the treatment of mild to severe AD, and is available as 5, 10, and 23 mg tablets. Donepezil is a reversible inhibitor of the enzyme AChE. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by AChE. While there is no evidence that donepezil alters the course of the underlying dementing process, 6 to 12-month controlled studies have shown modest cognitive and/or behavioral benefits in patients with AD.

Corium is developing Corplex™ Donepezil TDS, a matrix type transdermal patch that is designed for donepezil delivery over a 7-day wear period. A transdermal form of donepezil may benefit patients by potentially reducing gastrointestinal side effects (by bypassing the GI tract) and by improving treatment efficacy (through consistent, constant delivery, preventing missed doses and patient non-compliance).

3. OVERVIEW OF CLINICAL STUDIES

The clinical development program for Corplex™ Donepezil TDS consists currently of ten Phase 1 studies in healthy volunteers as shown in Table 1.

Table 1 List of Clinical Studies with Corplex™ Donepezil TDS

Study Category	Study Number	Study Title	Brief Objectives
Early Development	P-15007	A Phase 1 Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Two Formulations of a 7 -Day Application of Donepezil Transdermal Delivery System Compared to Oral Administration of Aricept in Healthy Volunteers	Assess initial TDS formulation performance
	P-15081	A Phase 1 Parallel Study to Evaluate the Pharmacokinetics (PK), Pharmacodynamics (PD) and Safety of Formulations of a 7-Day Application Donepezil Transdermal Delivery System (TDS) in Healthy Female Volunteers	Formulation Selection
	P-16007	A Phase 1 Study to Evaluate the Adhesion, Pharmacokinetics (PK) and Safety of a Seven-Day Application of Donepezil Transdermal Delivery System (TDS) in Healthy Volunteers	Adhesion Optimization
Key – Pivotal	P-15086	A Phase 1, Randomized, Open-Label, 3-Way Crossover, Pilot, Pharmacokinetic Study to Evaluate the Steady State Pharmacokinetics of a Once-Weekly Application of Corplex™ Donepezil Transdermal Delivery System Compared to Daily Oral Administration of Aricept® in Healthy Adult Subjects	Steady state Bioequivalence
Key – Supportive	P-16011	A Randomized Double-Blind Study to Assess the Skin Irritation and Sensitization Potential of Once-Weekly Corplex™ Donepezil Transdermal Delivery System	Skin Irritation/ Sensitization
	P-16012	A Phase 1, Crossover Study to Evaluate the Pharmacokinetics of Corplex™ Donepezil 10 mg Transdermal Delivery System Applied to Different Body Locations	Relative Bioavailability - Application Site (back, thigh, buttock)
	P-16039	A Phase 1, 2-Way Crossover Study to Evaluate the Effect of Heat Application on the Pharmacokinetics of Corplex™ Donepezil 5 mg Transdermal Delivery System (TDS) in Healthy Volunteers	Relative Bioavailability – Applied Heat
Supportive	P-16010	A Study to Assess the Steady State Bioequivalence of Once-Weekly Corplex™ Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®	Safety/Tolerability and Adhesion
	P-15086 Sub-Study[1]	A Phase 1, Randomized, Open-Label, 2-Way Crossover Study, to Compare the Relative Bioavailability of Two Corplex Donepezil Transdermal Delivery Systems' Manufactured Using Active Pharmaceutical Ingredient from 2 Different Suppliers	Relative Bioavailability - API Suppliers
	P-19005	A Phase 1, Randomized, Blinded, 2-Way Crossover Study to Assess the Relative Bioavailability of Corplex™ Donepezil Transdermal Delivery Systems With and Without Crystals	Relative Bioavailability – With vs Without Crystals

API = Active Pharmaceutical Ingredient

[1] The P-15086 Sub-Study was conducted as an amendment to Protocol No. P-15086.

Across all Phase 1 studies conducted to date with Donepezil and Corplex™ Donepezil TDS (any formulation), no safety concerns specific to Donepezil or Corplex™ Donepezil TDS have been identified. Most systemic adverse effects have been consistent with those described in the package insert for Aricept. Application site-related AEs accounted for the greatest differences in AEs reported with Corplex™ Donepezil TDS versus those reported with Aricept (due to the nature of transdermal delivery system). The most frequently reported AEs considered related to the TDS were nausea, headache, application site pruritus, application site erythema, and nightmare. Headache and

nausea were also observed following treatment with oral Aricept. Application site-related AEs were largely mild in severity and skin irritation assessments demonstrated that most application site irritation was scored as not detected or mild and decreased over wear duration. In studies of Corplex™ Donepezil TDS there were not apparent differences in the incidence and quality of AEs reported for subjects using regimens that titrated doses (5 mg/day initial dose) upward to the 10 mg/day target dose and those that did not titrate (initial dose was 10 mg/day). Both regimens yielded comparable adverse event profiles.

With regard to the pharmacokinetics of donepezil after Corplex™ Donepezil TDS application, of note is Study P-15086 wherein bioequivalence was demonstrated between the registration batch of the Corplex™ Donepezil TDS (TDS A) and oral Aricept®. The mean steady state donepezil plasma concentration-time profiles after weekly donepezil TDS application (TDS A, 10 mg/day) and daily oral 10 mg/day Aricept are shown in Figure 1. In accordance with the long donepezil half-life of approximately 70 hours, steady state was reached by Day 29, at the beginning of Week 5 during which the steady state exposure was evaluated. In line with the intension of the TDS application to also decrease the peak-to-through fluctuations of plasma donepezil concentrations, a lower donepezil C_{max} after the TDS application was observed compared to daily oral Aricept dosing. The mean steady-state donepezil concentrations after TDS application fell between the steady-state C_{max} and C_{min} after daily oral Aricept administration at most time points.

Corium has made changes to the intended commercial manufacturing process including changes to increase the bond strength between the active layer and the overlay portion of the patch. Since these and other changes may be considered major differences compared to the process used for the clinical batch used in Study P-15086, the purpose of the current study is to demonstrate bioequivalence at steady state between the highest strength (10 mg/day) TDS manufactured with the new manufacturing process and oral 10 mg/day Aricept®.

In clinical practice, some patients are taking 5 mg/day Aricept®, and donepezil-naïve patients typically receive 5 mg/day oral Aricept doses as a lead-in before safely escalating to a 10 mg/day dose. Therefore, Corium had also developed a 5 mg/day Corplex™ Donepezil TDS by using half the patch size as in the 10 mg/day TDS. The current study will therefore also evaluate the bioequivalence of steady-state donepezil plasma exposure (after dose-normalization) following once-weekly treatments with 5 mg/day Corplex™ Donepezil TDS compared to once-daily oral administration of 10 mg Aricept®. Bioequivalence is expected since it has been demonstrated that the pharmacokinetics of donepezil are linear over a dose range of 1-10 mg given once daily (Aricept® label, Eisai Inc, 2012). In addition, the 5-mg/day TDS application in the first study period for all subjects of the current study will allow safe escalation to 10 mg/day in the next study period.

Refer to the Investigator's Brochure (IB) for detailed background information on Corplex™ Donepezil TDS, and to the prescribing information for oral Aricept® (Aricept® label, Eisai Inc, 2018).

4. STUDY RATIONALE

The study is being conducted to evaluate the steady-state pharmacokinetics of 5 mg/day and 10 mg/day Corplex™ Donepezil TDS manufactured with the commercial process compared to 10 mg oral administration of Aricept® in healthy volunteers.

5. STUDY OBJECTIVES

5.1. Primary Objective

To evaluate the bioequivalence of steady-state donepezil plasma exposure following once-weekly treatments with 10 mg/day Corplex™ Donepezil TDS compared to once-daily oral administration of 10 mg Aricept®.

5.2. Secondary Objectives

- To evaluate the bioequivalence of steady-state donepezil plasma exposure (after dose-normalization) following once-weekly treatments with 5 mg/day Corplex™ Donepezil TDS compared to once-daily oral administration of 10 mg Aricept®.

- To evaluate the adhesion to the skin during the wear period of each once-weekly 5 mg/day and 10 mg/day Corplex™ Donepezil TDS application

5.3. Safety Objective

To evaluate the safety and tolerability, including local skin tolerability (Dermal Response and Other Effects) of once-weekly Corplex™ Donepezil TDS.

6. INVESTIGATIONAL PLAN

6.1. Study Design

This is a Phase 1, open-label, randomized, 3-period, 3-treament, crossover pharmacokinetic study to evaluate the steady-state pharmacokinetics of 5 mg/day and 10 mg/day Corplex™ Donepezil TDS manufactured with the commercial process compared to 10 mg oral administration of Aricept® in healthy volunteers.

The study will consist of a Screening Period, a Treatment Phase with 3 treatment periods and a Follow-Up Visit, as follows:

- **Screening Period:** Subjects will undergo a Screening Period up to 28 days prior to entering the Treatment Phase.

- **Treatment Phase:** Eligible subjects will participate in 3 treatment periods each consisting of 36 days, without a washout between treatments.

- **Treatment A:** 5 mg/day Donepezil Transdermal Delivery System (TDS) for 5 consecutive weeks (7-day wear for each of the 5 patches). In Period 1, all enrolled subjects will receive Treatment A. The last (5th) patch will be removed on the morning of Day 36 (168 hours after the last patch application). No study drug will be administered on Day 36. The 5 mg/day Donepezil TDS as the first treatment of the study allows subjects to get accustomed to the potential cholinergic effects (5 mg/day for 1 week is the recommended starting dose before titrating up, to 10 mg/day). In this study, the 5 mg/day Donepezil TDS is administered for 5 weeks to reach steady state in order to measure the steady state pharmacokinetics in Week 5 to be compared with those after oral Aricept®.

During Treatment Periods 2 and 3, the subjects will be randomized to receive either sequences of Treatments B-C or Treatments C-B. Subjects will receive the following treatments according to the randomization schedule.

- **Treatment B:** 10 mg/day Donepezil TDS applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks

- **Treatment C:** 10 mg Aricept® donepezil tablet administered QD for 5 weeks (within ±1 hour of dosing time on Day 1).

Randomization to the 2 treatment sequences will be stratified by the subject's gender. For all oral doses and TDS applications, subjects will receive a light meal 30 minutes prior to dosing. Standard meals will be provided at appropriate times thereafter. Blood samples for pharmacokinetics and safety assessments will be collected during the Treatment Phase.

In each period wherein the treatment consists of a patch, the subjects will wear a total of 5 patches for a total of 35 days (5 weeks). The last (5th) patch in the period will be removed after the morning blood draw on Day 36 (168-hour time point after the last patch in the period). No treatment will be administered on Day 36 of the period; additional post-wear PK blood samples will be collected on Day 36 after any patch treatment. Because of the lag time of donepezil plasma concentrations after TDS application, the C_{max} and T_{max} values at steady state. in some subjects, may be observed after removal of the TDS (past 168 hours after TDS application). This is the reason why an additional day (Day 36 in each treatment period) was added to the PK sampling schedule, after TDS removal at the end of the TDS dosing interval (168 hours).

In each period (Period 2 or 3) wherein the treatment consists of oral Aricept®, the subjects will an oral dose daily for a total of 35 days (5 weeks). The last oral dose in the period will be administered on the morning of Day 35. No treatment will be administered on Day 36 of the period; a PK blood sample will be collected in the morning of Day 36 at 24 hours after the last oral dose.

In Period 1, all subjects will wear patches (Treatment A). In Periods 2 and 3, subjects will either wear patches (Treatment B) or receive once-per-day oral Aricept® (Treatment C).

- The treatment in Period 2 will start on the morning of Study Day 37 after the pre-dose blood draw for Period 2 is collected. No treatment will be administered on Study Day 72. For the patch treatment in Period 2, the patch will be removed on Study Day 72 after the 168-hour blood sample collection.

- The treatment in Period 3 will start on the morning of Study Day 73 after the pre-dose blood draw for Period 3 is collected. No treatment will be administered on Study Day 108. For the patch treatment in Period 3, the patch will be removed on Study Day 108 after the 168-hour blood sample collection.

- **Follow-Up Visit:** 5 ±2 days after the day of the last oral drug administration or last TDS removal during the Treatment Phase, subjects will enter a Follow-Up Visit to evaluate safety parameters.

There will be no washout phase between treatment periods (with the exception of Day 36 within each period to collect post-treatment PK blood samples).

6.2. Study Duration

Subjects will participate in the study for up to 144 days, including up to 28 days of screening, a Treatment Phase with 3 treatment periods of 36 days each, and a 5 ±2 day Follow-Up Visit. Eligible subjects will stay in the research clinic for 109 days (108 overnight stays) during the Treatment Phase

7. SUBJECT SELECTION

7.1. Number of Subjects

An appropriate number of subjects will enter the Screening Period to enroll approximately 60 subjects to complete with 48 subjects during the Treatment Phase.

7.2. Study Population

Healthy male and female subjects who meet the inclusion/exclusion criteria listed below.

7.2.1. Inclusion Criteria

A subject will be eligible for inclusion in the study if all the following criteria apply:

1. Healthy males and females.

2. Subject must be a male or non-pregnant, non-breastfeeding female.

3. Subject must be between 18 and 55 years of age (inclusive) at Screening.

4. Subject's Body Mass Index (BMI) must be between 18 and 32 kg/m2 (inclusive) and subject must weigh between 60 and 100 kg (inclusive) at Screening.

5. Subject must be continuous non-smokers and agree not to smoke during confinement and from the time of screening and throughout the study.

6. Subject must have a Fitzpatrick skin type of I, II or III or have skin colorimeter scores equivalent to the allowed Fitzpatrick skin type.

7. Female subjects must agree to use one of the following forms of birth control from screening until 14 days after the End-of-Study Visit, unless a different timeframe is listed below:

   a) Vasectomized partner (at least 6 months prior to Screening).

   b) Post-menopausal (at least 2 years prior to Screening).

   c) Surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to Screening.

   d) Non-surgical sterilization (e.g., Essure® procedure) at least 3 months prior to Screening.

   e) Double barrier (diaphragm with spermicide; condoms with spermicide)

   f) Intrauterine device (IUD)

   g) Total abstinence (must agree to use a double barrier method if they become sexually active between Screening and 14 days after the End-of-Study Visit).

   h) Implanted or intrauterine hormonal contraceptives in use for at least 3 consecutive months prior to Screening.

   i) Oral, patch, or injected contraceptives, or vaginal hormonal device (i.e., NuvaRing®), in use for at least 3 consecutive months prior to Screening.

8. Subject must be able to speak, read and understand English or Spanish.

9. Subject must voluntarily consent to participate in this study and provide their written informed consent prior to start of any study-specific procedures

10. Subject is willing and able to remain in the study unit for the entire duration of each confinement period and return for the Follow-Up Visit.

7.2.2. Exclusion Criteria

A subject who meets any of the following exclusion criteria will not be enrolled into the study:

1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.

2. More specifically, subjects with a history of serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other cardiac problems.

3. More specifically, at the discretion of the Investigator, subjects with preexisting hypertension, heart failure, myocardial infarction, or ventricular arrhythmia/prior EEG abnormalities in absence of seizure.

4. At the discretion of the Investigator, a clinically significant abnormal finding in the physical examination, vital signs, medical history (including a family history of sudden death/ventricular arrhythmia), electrocardiogram (ECG), or clinical laboratory results at Screening.

5. After resting seated for at least 3 minutes, subjects should be excluded from the study with the following vital signs at Screening:

    a) a confirmed systolic blood pressure outside the range of 90-145 mmHg, or
    b) a confirmed diastolic blood pressure outside the range of 50-90 mmHg, or
    c) a confirmed resting heart rate outside the range of 40-100 beats per minute.

6. Has an isolated alanine aminotransferase (ALT) ≥1.5x the Upper Limit of Normal (ULN) or aspartate aminotransferase (AST) ≥1.5x the ULN at Screening; or both ALT and AST exceeding the ULN.

7. Estimated creatinine clearance at screening <70 mL/min/1.73 m^2 using the CKD-EPI equation calculator (Levey 2009).

8. Prolonged corrected QT interval by Fridericia's formula (QTcF) on screening electrocardiogram (ECG) (≥450 ms for both females and males).

9. History of significant multiple and/or severe allergies (e.g., latex allergy, band aids, adhesive dressing, or medical grade adhesive tape), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs.

10. Major surgery that required general anesthesia within 90 days prior to Screening.

11. History or presence of hypersensitivity or idiosyncratic reaction to the study drugs or related compounds (including piperidine derivatives and other cholinesterase inhibitors).

12. At the discretion of the Investigator, on a significantly abnormal diet during the 4 weeks preceding Day -1.

13. History or presence of excessive hairy skin on application sites as deemed by the Investigator to potentially interfere with patch adhesion or drug absorption.

14. History or presence of significant skin damage, diffuse skin diseases (e.g., diffuse psoriasis or eczema), scars (flat scars, birth marks, moles, and stretch marks that do not affect skin surface are allowed), tattoos on the application sites or other skin disturbances (including sunburns, excessive tanning, and stretch marks) as deemed by the Investigator to potentially interfere with drug absorption or skin tolerability assessments

15. Use of donepezil hydrochloride or related drugs within 60 days prior to the first study drug administration (oral administration or TDS application, as appropriate).

16. Has donated ≥500 mL blood within 30 days or donated ≥500 mL plasma within 14 days prior to Day -1.

17. Inadequate peripheral venous access that would interfere with obtaining blood samples.

18. Has participated in another clinical trial (randomized subjects only) within 30 days prior to Day -1.

19. Has used any over the counter (OTC) medication, including vitamins, herbal products, and dietary supplements within 14 days prior to Day -1.

20. Has used any prescription medication, except hormonal contraceptive or hormonal replacement therapy, within 14 days prior to Day -1.

21. Has a history of substance abuse or treatment (including alcohol) within 1 year prior to Screening.

22. Is a female with a positive pregnancy test.

23. Has a positive urine screen for drugs of abuse at Screening or Day -1.

24. Has a positive urine screen for alcohol on Screening or Day -1.

25. Has a positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody at Screening or has been previously treated for hepatitis B, hepatitis C, or HIV infection.

26. Has an active COVID-19 test at Screening or Day -1.

27. Has clinically significant gastrointestinal problems, including narrowing of the

gastrointestinal tract, that may interfere with the gastrointestinal absorption of study drug.

28. History of eating disorders within 3 months prior to Day -1.

29. Has a history of unstable psychiatric illness requiring medications or hospitalization within 12 months prior to Day -1, or exhibits marked anxiety, tension, or agitation.

30. Specifically, diagnosis of comorbid bipolar disorder/comorbid depressive symptoms.

31. Has a history of unexplained syncope.

32. Subject has any history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, at Screening or Day -1.

33. Has smoked or used tobacco products within 6 months prior to Day -1 or is currently using nicotine products; is unable to abstain from the use of any nicotine-containing products (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges).

34. Subject is an employee or relative of any employee working for the CRO or the Sponsor.

8. STUDY TREATMENTS

8.1. Study Drug Treatments

On Day -1, eligible subjects will be checked into the research clinic to enter the Treatment Phase.

The study treatments are as follows:

Treatment A (Test): 5 mg/day Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each). All subjects will receive Treatment A in Period 1. The patch will be removed on the morning of Day 36.

At the start of Period 2, subjects will be randomized to one of the following treatments in Period 2. Subjects will receive the alternate treatment in Period 3. Randomization to the 2 treatment sequences will be stratified by gender.

Treatment B (Test): 10 mg/day Corplex™ Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each).

Treatment C (Reference): 10 mg Aricept® donepezil (1 x 10 mg/day tablet) administered QD for 35 consecutive days (within ±1 hour of dosing time on Day 1). This is the Reference Listed Drug

(RLD).See Section 2 for a treatment phase schematic.

TDS Application: The first patch in each period with patch treatments (Treatment A or B) will be applied on Treatment Phase Days 1, 37, and 73. For patches #2 to #4, at the end of each week of patch wear (168 h after application), the worn patch will be removed and a new patch will be applied. The 168-h post-dose PK blood samples will be collected before removal of the worn patch.

The last (5th) patch in each period with patch treatments (Treatment A or B) will be removed after 168 hours of the last patch application, after the 168-h PK blood sample collection.

Oral Dosing: In periods with oral Aricept (Treatment C), a single dose will be administered daily on Treatment Phase Days 37-71 (Period 2) and 73-107 (Period 3).

Drug-Free Days: There is no study drug administration (neither patch wear nor oral dosing) on Treatment Phase Days 36, 72, and 108.

In each period wherein the treatment consists of a patch, the subjects will wear a total of 5 patches for a total of 35 days (5 weeks). The last (5th) patch in the period will be removed after the morning blood draw on Day 36 (168-hour time point). No treatment will be administered on Day 36 of the period; additional post-wear PK blood samples will be collected on Day 36 after any patch treatment.

In Period 1, all subjects will wear patches (Treatment A). In Periods 2 and 3, subjects will either wear patches (Treatment B) or receive once-per-day oral Aricept® (Treatment C).

The treatment in Period 2 will start on the morning of Study Day 37 after the pre-dose blood draw for Period 2 is collected. No treatment will be administered on Study Day 72. For the patch treatment in Period 2, the patch will be removed on Study Day 72 after the 168-hour blood sample collection.

The treatment in Period 3 will start on the morning of Study Day 73 after the pre-dose blood draw for Period 3 is collected. No treatment will be administered on Study Day 108. For the patch treatment in Period 3, the patch will be removed on Study Day 108 after the 168-hour blood sample collection.

TDS Administration (Treatments A and B):

The pharmacy at the CRU will remove the TDS from refrigerated storage (2-8ºC) and place at room temperature storage (20-25ºC) on the day before application, no more than 24 hours prior to application. The pharmacy at the CRU will prepare the Corplex™ Donepezil TDS for each subject (per the randomization and stratification scheme). Each TDS treatment will be applied to intact dry skin only on the subject's back weekly for 5 consecutive weeks. The most ideal naïve location on the back (back area that avoids the bra area and is slightly above the waistline is preferred) should

be reserved for the last TDS application of each period. If this is not possible Sponsor approval should be obtained and documented to apply the TDS to a previously used site.

- It is recommended that the TDS is applied to the subject within 120 minutes of opening/removing from the packaging.

- Subjects will be instructed to shower from 1 to 2 hours prior to each TDS application. No more than 1 shower a day is permitted and if showers are not taken, the following will be performed within 1 to 2 hours prior to each TDS application, the application area will be washed with room temperature water using a wet washcloth. The application site will be patted dry and will be checked for irritancy.

- The application area will be identified with a template overlay. The TDS will be placed at the designated application site and firm pressure will be applied immediately over the TDS for approximately 20 seconds using the palm of the hand on each TDS to ensure adhesion. A new TDS should not be applied to an area of skin where a TDS was just removed. The area selected should not be oily, damaged, or irritated and should not be exposed to sunlight.

- No taping of the transdermal delivery systems will be allowed.

- The exact clock time of TDS application and removal will be recorded for the start and end of TDS application. During each TDS treatment, the next TDS will be applied as soon as the previous TDS was removed. The change in TDSs should be performed within 15 minutes.

Oral Drug Administration (Treatment C):

Study drug will be given orally and be administered with approximately 240 mL of water. Subjects will be instructed not to crush, split, or chew the study drug tablets.

8.2. Treatment Assignment

At the start of Period 2, subjects will be randomized to one of the following treatments in Period 2. Subjects will receive the alternate treatment in Period 3. Randomization to the 2 treatment sequences will be stratified by gender using a computer-generated randomization scheme. Study drug will be assigned to each subject on each dosing day based on the randomization scheme.

8.3. Blinding

This is an open-label pharmacokinetic study; therefore, study treatments will not be blinded.

8.4. Compliance

Each dose of study drug will be administered in the research clinic by a pharmacy staff member or

Investigator-delegated employee. A record of the dosing event will be prepared and kept by the clinical site.

9. STUDY PROCEDURES

The study will consist of a Screening Period, a Treatment Phase and a Follow-Up Visit. A table with the Schedule of Events (SOE) representing the required testing procedures to be performed is included in **Section 1**. Following is a list of these procedures and assessments:

9.1. Screening Procedures

Subjects will complete the screening visit within 28 days (Day -28 to Day -1) of admission to the in-clinic visit of the Treatment Phase (Day -1). Prior to conducting any study-related activities including screening procedures, written Informed Consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

The following information collection/assessments will be performed at the Screening Visit:

1. Informed Consent and HIPAA authorization by the subject.
2. Subject demographics including date of birth, sex, race, and ethnicity.
3. Review of inclusion/exclusion criteria to determine study eligibility.
4. Record medical history including skin type assessment, chronic conditions, relevant surgical procedures (with start date) history of alcohol and recreational drug use, smoking status, evaluation of drug and alcohol use and personal habits affecting the skin (example: tanning, hair removal, and application of tattoos).
5. Fitzpatrick skin type score: Type I - always burns, never tans, Type II - usually burns, tans with difficulty, or Type III - may burn initially, but tans easily.
6. A complete physical examination with back evaluation and personal habits affecting the skin (example: tanning, hair removal, and application of tattoos).
7. Body weight, height, and BMI.
8. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).
9. 12-lead electrocardiogram (ECG) after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF).

10. Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis) obtained under fasted conditions. During the Screening Period, Clinical Laboratory Measurements may be repeated at the discretion of the Investigator.

11. Blood samples for Serology (HIV antibody, hepatitis B surface antigen and hepatitis C virus antibody).

12. Urine samples will be tested for alcohol, drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and opioids) If the test is positive for any of the tested analytes, the subject will be excluded from study participation.

13. Coronavirus (COVID-19) test. A diagnostic test to determine if an active coronavirus infection is present.

14. A serum β-hCG pregnancy test will be performed. A positive pregnancy test will exclude a subject from enrollment into the study.

15. Perform the Columbia Suicide Severity Rating Scale (C-SSRS), "Baseline" version. Subjects with a history of attempted suicide or clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from enrollment in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

16. Review of concomitant medications, treatment and/or therapies.

After subjects complete the screening procedures and are considered eligible to take part in the clinical study, they will be instructed to return to the clinic to begin the Treatment Phase.

9.2. Check-In Procedures (Day -1)

Subjects who meet the inclusion/exclusion criteria during Screening, will be checked into the research clinic on Day -1, the day before treatment with study drug. Subjects will undergo the following procedures upon check-in:

1. Review of inclusion/exclusion criteria to determine whether subjects continue to meet study eligibility.

2. Update medical history.

3. Back application site evaluation and clip application site hair as needed.

4. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature). Vital signs will be taken at least 12 hours prior to the

subject receiving their first dose of study drug on Day 1.

5. 12-lead electrocardiogram (ECG) after subject has been in supine position for a minimum of 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF).

6. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) "Since Last Visit" version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

7. Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis) will be obtained.

8. Urine samples will be tested for alcohol, cotinine, drugs of abuse: (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and opioids) If the test is positive for any of the tested analytes, the subject will be excluded from study participation.

9. Coronavirus (COVID-19) test. A diagnostic test to determine if an active coronavirus infection is present. If the test is for the virus is detected, the subject will be excluded from study participation

10. A urine pregnancy test will be performed. A positive pregnancy test will exclude a subject from enrollment into the study.

11. Review of concomitant medications, treatment and/or therapies.

9.3. In-Clinic Procedures Treatment Phase

Subjects will stay in the research clinic during the Treatment Phase for 109 days (108 overnight stays) starting on Day -1. The Treatment Phase will consist of 3 treatment periods of 36 days each, and a 5 ±2 day Follow-Up Visit. Subjects will be discharged from the clinical unit on Day 109.

9.3.1. Study Drug Administration

On Day 1 of Period 1 during the Treatment Phase, subjects will receive the following treatment:

Treatment A (Test): 5 mg/day Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each). All subjects will receive Treatment A in Period 1. The patch will be removed on the morning of

Day 36.

At the start of Period 2, subjects will be randomized to one of the following treatments in Period 2. Subjects will receive the alternate treatment in Period 3. Randomization to the 2 treatment sequences will be stratified by gender.

Treatment B (Test): 10 mg/day Corplex™ Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each).

Treatment C (Reference): 10 mg Aricept® donepezil (1 x 10 mg/day tablet) administered QD for 35 consecutive days (within ±1 hour of dosing time on Day 1). This is the Reference Listed Drug (RLD).

In each period wherein the treatment consists of a patch, the subjects will wear a total of 5 patches for a total of 35 days (5 weeks). The last (5th) patch in the period will be removed after the morning blood draw on Day 36 (168-hour time point). No treatment will be administered on Day 36 of the period; additional post-wear PK blood samples will be collected on Day 36 after any patch treatment.

In each period wherein the treatment consists of oral Aricept®, the subjects will an oral dose daily for a total of 35 days (5 weeks). The last oral dose in the period will be administered on the morning of Day 35. No treatment will be administered on Day 36 of the period; a PK blood sample will be collected in the morning of Day 36 at 24 hours after the last oral dose. In Periods 2 and 3, subjects will either wear patches (Treatment B) or receive once-per-day oral Aricept® (Treatment C).

- The treatment in Period 2 will start on the morning of Study Day 37 after the pre-dose blood draw for Period 2 is collected. No treatment will be administered on Study Day 72. For the patch treatment in Period 2, the patch will be removed on Study Day 72 after the 168-hour blood sample collection.

- The treatment in Period 3 will start on the morning of Study Day 73 after the pre-dose blood draw for Period 3 is collected. No treatment will be administered on Study Day 108. For the patch treatment in Period 3, the patch will be removed on Study Day 108 after the 168-hour blood sample collection.

TDS Administration (Treatments A and B):

- The pharmacy at the CRU will remove the TDS from refrigerated storage (2-8ºC) and place at room temperature storage (20-25ºC) on the day before application, no more than 24 hours prior to application.

- The pharmacy at the CRU will prepare the Corplex™ Donepezil TDS for each subject (per

the randomization and stratification scheme). Each TDS treatment will be applied to intact dry skin only on the subject's back weekly for 5 consecutive weeks. The most ideal naïve location on the back (back area that avoids the bra area and is slightly above the waistline is preferred) should be reserved for the last TDS application. If this is not possible Sponsor approval should be obtained and documented to apply the TDS to a previously used site.

- It is recommended that the TDS is applied to the subject within 120 minutes of opening/removing from the packaging.

- Subjects will be instructed to shower from 1 to 2 hours prior to each TDS application. No more than 1 shower a day is permitted and if showers are not taken, the following will be performed within 1 to 2 hours prior to each TDS application, the application area will be washed with room temperature water using a wet washcloth. The application site will be patted dry and will be checked for irritancy.

- The application area will be identified with a template overlay. The TDS will be placed at the designated application site and firm pressure will be applied immediately over the TDS for approximately 20 seconds using the palm of the hand on each TDS to ensure adhesion. A new TDS should not be applied to an area of skin where a TDS was just removed. The area selected should not be oily, damaged, or irritated and should not be exposed to sunlight.

- No taping of the transdermal delivery systems will be allowed.

- The exact clock time of TDS application and removal will be recorded for the start and end of TDS application. During each TDS treatment, the next TDS will be applied as soon as the previous TDS was removed. The change in TDSs should be performed within 15 minutes.

Oral Drug Administration (Treatment C):

Study drug will be given orally and be administered with approximately 240 mL of water. Subjects will be instructed not to crush, split, or chew the study drug tablets

The pharmacy manual will provide further application information.

9.3.2. Procedures on Dosing Days (Days 1, 8, 15, 22, & 29) during Period 1

The following assessments will be performed on dosing days during Period 1 of Treatment Phase:

1. Subjects will be instructed to shower from 1 to 2 hours prior to each TDS application. If showers are not taken, the following will be performed within 1 to 2 hours prior to each TDS application, the application area will be washed with room temperature water using a wet washcloth. The application site will be patted dry and will be checked for irritancy.

2. Subjects will receive a light meal approximately 30 minutes prior to TDS application or oral Aricept administration.

3. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, oral temperature) will be collected at times listed in **Section 13.4**.

4. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1**.

5. The site receiving the TDS should be assessed for skin irritation prior to TDS application (if the score is greater than zero another site must be selected).

6. The TDS is applied to the subject within 120 minutes of opening/removing from the packaging and the application area will be identified with a template overlay. The TDS will be placed at the designated application site and firm pressure will be applied immediately over the TDS for approximately 20 seconds using the palm of the hand on each TDS to ensure adhesion. The area selected should not be oily, damaged, or irritated and should not be exposed to sunlight. The exact clock time of TDS application will be recorded for the start of TDS application. No taping of the Transdermal Delivery Systems will be allowed.

7. A photograph of the TDS will be taken immediately after application and at all adhesion timepoints.

8. Patch Adhesion Assessments will be performed at times listed in **Section 15.1**.

9. Review of concomitant medications, treatment and/or therapies.

10. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8.** The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points.

The PK samples will be collected at the nominal time points ±5 minutes.

9.3.3. Procedures for In-Clinic Days during Period 1

The following assessments will be performed during the in-clinic days of period 1:

1. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1**.

2. TDS Adhesion Assessments will be performed at times listed in **Section 15.0.**

3. A photograph of the TDS will be taken at adhesion timepoints.

4. Review of concomitant medications, treatment and/or therapies

5. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8**. The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points.

9.4. Procedures on TDS Removal Days (Days 8, 15, 22, 29 & 36) during Period 1

1. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, oral temperature) will be collected at times listed in **Section 13.4.**

2. Immediately after removal, used TDSs will be collected and returned to the Sponsor. As soon as the TDS has been removed from the skin, the used TDS will be placed, adhesive side down, on to a new release liner or folded in half and placed into a foil pouch. The sealed, labeled foil pouch and the corresponding original labeled patch pouch will then be inserted into a plastic bag and stored at approximately -20°C (-4°F) The used TDS will be shipped to the Sponsor, for residual drug determination. Additional instructions regarding application and removal of the TDS are provided in the Pharmacy Manual.

3. TDS site Irritation Assessments will be obtained at times listed in **Section 16.1.**

4. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1.**

5. Obtain blood sample for chemistry, hematology, coagulation, and urinalysis tests. (Day 36).

6. Urine pregnancy tests for females only (Day 36).

7. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) “Since Last Visit” version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator (Day 36).

8. Patch Adhesion Assessments and photographs will be performed at times listed in **Section 15.0**

9. Review of concomitant medications, treatment and/or therapies

10. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8.** The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points.

9.4.1. Study Drug Administration (Period 2 & 3) Treatment B

The following assessments will be performed on dosing days during Period 2 & 3 of Treatment B Phase (**Study Days 37, 44, 51, 58, 65, 73, 80, 87, 94, & 101**):

1. Subjects will be instructed to shower from 1 to 2 hours prior to each TDS application. If showers are not taken, the following will be performed within 1 to 2 hours prior to each TDS application, the application area will be washed with room temperature water using a wet washcloth. The application site will be patted dry and will be checked for irritancy.

2. Subjects will receive a light meal approximately 30 minutes prior to TDS application

3. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, oral temperature) will be collected at times listed in **Section 13.4**.

4. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1.**

5. The site receiving the TDS should be assessed for skin irritation prior to TDS application (if the score is greater than zero another site must be selected).

6. The TDS is applied to the subject within 120 minutes of opening/removing from the packaging and the application area will be identified with a template overlay. The TDS will be placed at the designated application site and firm pressure will be applied immediately over the TDS for approximately 20 seconds using the palm of the hand on each TDS to ensure adhesion. The area selected should not be oily, damaged, or irritated and should not be exposed to sunlight. The exact clock time of TDS application will be recorded for the start of TDS application. No taping of the Transdermal Delivery Systems will be allowed.

7. A photograph of the TDS will be taken immediately after application and at adhesion timepoints listed in **Section 15.0.**

8. Patch Adhesion Assessments will be performed at times listed in **Section 15.0**

9. Review of concomitant medications, treatment and/or therapies.

10. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8.** The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points.

The PK samples will be collected at the nominal time points ±5 minutes.

9.4.2. Procedures on In-Clinic Days Period 2 & 3 Treatment B & C

The following assessments will be performed during the in-clinic days of Periods 2 &3:

1. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1**.

2. TDS Adhesion Assessments will be performed at times listed in **Section 15.0 Treatment B only.** A photograph of the TDS will be taken at adhesion timepoints listed in **Section 15.0 Treatment B only**

3. Review of concomitant medications, treatment and/or therapies

4. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8**. The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points.

9.4.3. Procedures on TDS Removal Day Treatment B Periods 2 & 3 (Days 44, 51, 58, 65, 72, 80, 87, 94, 101, 108):

1. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, oral temperature) will be collected at times listed in **Section 13.4.**

2. Immediately after removal, used TDSs will be collected and returned to the Sponsor. As soon as the TDS has been removed from the skin, the used TDS will be placed, adhesive side down, on to a new release liner or folded in half and placed into a foil pouch. The sealed, labeled foil pouch and the corresponding original labeled patch pouch will then be inserted into a plastic bag and stored at approximately -20°C (-4°F). The used TDS will be shipped to the Sponsor, for potential residual drug determination. Additional instructions regarding application and removal of the TDS are provided in the Pharmacy Manual.

3. TDS site Irritation Assessments will be obtained at times listed in **Section 16.0**

4. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1.**

5. Obtain blood sample for chemistry, hematology, coagulation, and urinalysis tests. (Day 72).

6. Urine pregnancy tests for females only (Day 72).

7. Perform the Columbia Suicide Severity Rating Scale (C-SSRS) “Since Last Visit” version. Subjects with clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, will be excluded from further participation in the study, and further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator (Day 72).

8. Patch Adhesion Assessments and photographs will be performed at times listed in **Section 15.0.**

9. Review of concomitant medications, treatment and/or therapies

10. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8.** The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points

9.4.4. Procedures for Drug Administration Treatment C (Period 2 & 3)

The following assessments will be performed for drug administration for during Period 2 & 3):

1. Subjects will receive a light meal approximately 30 minutes prior to drug administration.

2. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, oral temperature) will be collected at times listed in **Section 13.4**.

3. Blood samples for pharmacokinetics will be collected at times listed in **Section 14.1**.

4. Randomized subjects will receive 10 mg Aricept® donepezil (1 x 10 mg/day tablet) administered QD for 35 consecutive days during either Period 2 or Period 3. Study drug will be given orally and be administered with approximately 240 mL of water. Subjects will be instructed not to crush, split, or chew the study drug tablets.

5. Water will be allowed ad libitum up to 1 hour prior to dose administration. No water maybe consumed for 1-hour prior through 1 hour after dosing (except for water needed to administer study drug). After 1 hour following dose administration, subjects may drink water ad libitum.

6. Review of concomitant medications, treatment and/or therapies.

7. Assessment of adverse events. While subjects are in the research clinic, AEs will be monitored continuously and solicited using a non-leading question at times listed in **Section 13.8.** The inquiry using non-leading questions will be performed after all other procedures are conducted for the specified time points.

9.4.5. End of Treatment (Day 109)

The end of the treatment phases of the study is Day 109. After all procedures during the Treatment Phase are conducted including the collection of the 168-hour blood sample after the last dose of study drug, the following End-of-Treatment procedures will be conducted:

1. Complete physical examination.
2. Body weight.
3. Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis). Samples for clinical laboratory tests at the end of treatment can be collected under non-fasted conditions.
4. Urine pregnancy test (females only).
5. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, oral temperature).
6. 12-lead ECG will be obtained after the subject has been in the supine position for at least 3 minutes.
7. Assessment of the Columbia Suicide Severity Rating Scale (C-SSRS), "Since Last Visit" version. If a subject has a clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.
8. Review of concomitant medications, treatment and/or therapies.
9. Assessment of adverse events.

Subjects will be discharged from the research clinic when the Investigator determines that the subjects are medically stable, and all end-of-treatment procedures are completed.

9.5. Unscheduled Assessments and Early Termination Visits

9.5.1. Unscheduled Assessments

Unscheduled visits occur at any unplanned subject evaluation during study conduct not specified in the Schedule of Events or overall protocol and will be documented and recorded in the database and listings. Unscheduled assessments during study conduct will be inclusive of, but not limited to TDS removals, TDS applications, adhesion assessments, adhesion photographs, and skin tolerability assessments.

9.5.2. Early Termination (ET)

Early Termination (ET) from the study is defined as withdrawal during the Treatment Phase after at least one dose of study drug is administered. The ET Visit is not required for subjects who screen fail before the administration of the first dose of study drug.
If possible, subjects who terminate early will complete all study procedures post-dose study drug (including PK sample collections) before starting ET procedures. The following procedures will

be performed at ET visits:

1. Complete physical examination.

2. Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) after subject has been sitting for a minimum of 3 minutes.

3. 12-lead ECG after subject has been in supine position for a minimum of 3 minutes.

4. Clinical laboratory tests (chemistry, hematology coagulation, and urinalysis). Samples for clinical laboratory tests at Early Termination can be collected under non-fasted conditions.

5. Urine pregnancy tests (for females only)

6. Assessment of the Columbia Suicide Severity Rating Scale (C-SSRS), "Since Last Visit" version. If a subject has a clinically significant suicidal ideation based on the C-SSRS assessment, in the opinion of the Investigator, further evaluation and/or preventive intervention steps for suicidal behavior will be taken, at the discretion of the Investigator.

7. If applicable, perform skin irritation/tolerability assessments, adhesion assessments and adhesion photographs.

8. Review of concomitant medications, treatment and/or therapies.

9. Assessment of adverse events.

Subjects will be discharged from the study clinic when the Investigator determines that the subjects are medically stable and, if possible, after all ET procedures are completed.
At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day as part of the procedures of the current treatment phase, do not need to be repeated.
Subjects who withdraw early from the study and complete the above ET procedures will not return for a Follow-Up Visit. Therefore, the ET Visit is the EOS for these subjects.

9.6. Follow-Up Visit

Subjects who complete the Treatment Phase will return in 5 ±2 days after the administration of the last dose of study drug for the Follow-Up Visit.

The following procedures will be completed during the Follow-Up Visit:

1. Complete physical examination.

2. Vital signs after a minimum of 3 minutes of rest (respiratory rate, pulse rate, blood pressure, and oral temperature).

3. 12-lead ECG after the subject has been supine at least 3 minutes.
4. If applicable, perform skin irritation/tolerability assessments.
5. Review of concomitant medications, treatment and/or therapies.
6. Assessment of adverse events.

The Follow-Up Visit is the EOS for subjects who will undergo the Follow-Up procedures.

9.7. End of Study (EOS)

The End of Study (EOS) is either the Follow-Up Visit for subjects who complete the Treatment Phase, or the Early Termination Visit for subjects who withdraw early from the study.

10. CONCOMITANT MEDICATIONS AND RESTRICTIONS

Subjects will be instructed not to consume any of the below products; however, allowance for an isolated single incidental consumption may be evaluated and approved by the study Investigator based on the potential for interaction with the study drug, and impact on subject safety and the validity of the study results.

10.1. Concurrent Medication Restrictions

Restricted Medications:

1. Any OTC medication use within 14 days prior to Day -1 until the End-of-Study Visit without evaluation and approval by the study Investigator. With approval of the Investigator, acetaminophen may be given as needed during the study as rescue medication to treat headaches or other adverse events.
2. Subject must not take any prescription medication, with the exception of female hormonal contraceptives, from 14 days prior to Day -1 until the End-of-Study Visit without evaluation and approval by the Investigator.

All other concomitant medications will be prohibited unless its use is deemed necessary in a medical emergency. Concomitant use of prescription or nonprescription medications, including reasons for use, will be reviewed, and recorded on the eCRF from the Screening Period through the Follow-up Period.

Allowed concurrent medications can be taken with water if needed, irrespective of the water restrictions before and after administration of study drug.

10.2. Dietary Restrictions

While subjects are in the research clinic, the following dietary restrictions will be followed:

1. Subjects must not take any herbal or dietary supplements (e.g., St. John's Wort, Milk Thistle, etc.) within 14 days prior to Day -1 until the End-of- Study Visit.

2. Subjects must not consume beverages and foods containing alcohol or caffeine/xanthine from 48 hours prior to Day -1 until after discharge on Day 109. Alcohol and caffeinated beverages will not be available while in the research clinic.

3. Water Consumption: Water will be allowed ad libitum up to 1 hour prior to dose administration. For Treatment C (Aricept 10 mg), after 1 hour following dose administration, subjects may drink water ad libitum. Fluids during the predose light meal are allowed.

4. Food Consumption: While housed in the research clinic, subjects will receive meals at regularly scheduled times. No food sharing will be permitted. Standard meals will be provided at appropriate times. Calories will be spread across the day. Mealtimes may be adjusted to not interfere with study procedures such as blood draws for pharmacokinetics.

10.3. General Restrictions

1. Subject must not engage in strenuous activities such as exercise or sports within 24 hours prior to Day -1 until the End-of-Study Visit.

2. No more than 1 shower a day is permitted. Subjects must avoid having the water spray directly on the patch. Water running over the patch is allowed. The patch should be patted dry after the shower.

3. Subject must not donate blood (one pint or more) from 30 days or plasma from 14 days prior to Day -1 until the End-of-Study Visit. It is recommended that blood/plasma donations not be made for at least 30 days after the End-of-Study Visit.

4. Subjects must not smoke or use tobacco products from 6 months prior to Day -1 until the End-of-Study Visit. Subjects must refrain from use of all nicotine products (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges) from Screening until the End-of-Study Visit.

5. Female subjects must utilize one of the allowed forms of birth control listed in the Inclusion Criteria (**Section 8.2.1**).

6. Following all TDS applications, subjects will remain seated in chairs without the following back support: pillows, soft padding, blankets, or similar; for at least the first 2 hours, except

when they are supine or standing for study procedures. Subjects will then resume normal activity. During the first 2 hours post dose, subjects may be allowed to rise for brief periods under supervision (e.g., in order to use the toilet facilities). However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their side.

7. Following oral drug administration (Treatment C) subjects will remain seated, except as otherwise required for study procedures or personal needs, for the first 4 hours after dosing. Subjects will not be allowed to lie down, except as directed by clinical staff secondary to adverse events, for the first 4 hours after dosing.

11. INVESTIGATIONAL PRODUCT

11.1. Active Pharmaceutical Ingredients

Corplex™ Donepezil Transdermal Delivery System (TDS) is a matrix type transdermal patch manufactured for a 7-day application.

11.2. Pharmaceutical Treatments

Treatment A (Test): 5 mg/day Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each). All subjects will receive Treatment A in Period 1. The patch will be removed on the morning of Day 36.

At the start of Period 2, subjects will be randomized to one of the following treatments in Period 2. Subjects will receive the alternate treatment in Period 3. Randomization to the 2 treatment sequences will be stratified by gender.

Treatment B (Test): 10 mg/day Corplex™ Donepezil TDS manufactured with the commercial process applied weekly (within ±1 hour of application time on Day 1) for 5 consecutive weeks (7-day wear each).

Treatment C (Reference): 10 mg Aricept® donepezil (1 x 10 mg/day tablet) administered QD for 35 consecutive days (within ±1 hour of dosing time on Day 1). This is the Reference Listed Drug (RLD).

11.3. Supply of Study Drug

The Sponsor (or designee) will ship study drug to the investigational site. The study drug shipment(s) will be shipped after site activation. All other drug products needed for the conduct of the study (such as medications to treat Adverse Events) will be commercially available products obtained by the research clinic.

11.4. Packaging and Labeling

The investigation product will be packaged and labeled appropriately, according to the appropriate FDA regulations. See the Pharmacy Manual for details of packaging and labeling.

11.5. Materials Control

Once received and labeled by the onsite pharmacist or designee for use in the study, the drugs will be considered study drug material. The pharmacist or designee will maintain adequate records of the receipt, dispensing, return or other disposition of the drug, including dates, quantity, serial numbers, expiration dates, as appropriate. Reasons for any departure from the expected regimen will be documented. These documents will be made available to regulatory agency inspectors upon request. The Investigator will not supply study drug to anyone other than those named as sub-investigators on FDA Form 1572, designated site staff, and subjects in the study.

11.6. Storage of Study Drug

Study drug for Treatment A and B will be stored at a controlled; refrigerated temperature (2-8ºC). The pharmacy will remove the TDS from 2-8ºC refrigerated storage on the day before application and no more than 24 hours prior to application, and stored at controlled room temperature of 20-25°C (68-77°F) with excursions allowed between 15° and 30°C (59° and 86°F). Transient spikes up to 40°C are permitted as long as they do not last for more than 24 hours. Study drug will be stored in a safe, secure area with limited, controlled access in accordance with all local, state, and federal regulations. Investigational products must not be frozen. The Investigator will ensure that adequate precautions are taken, including storage of the study drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product.

11.7. Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

12. SAFETY ASSESSMENT

12.1. Medical History

A complete medical history will be obtained at the Screening Visit including the recording of demographic data (date of birth, sex, age, race, ethnicity), collection of previous surgeries, medications and chronic conditions, past or present illnesses or dysfunctions, substance/drug abuse, and history of allergies or idiosyncratic responses to drugs.

12.2. Physical Examination

A complete physical examination including body weight will be completed for all subjects at Screening, at End-of-Treatment or Early Termination, and at the Follow-Up visits. The complete physical examination will include a review of the subject's general appearance, skin, head and neck (eyes, ears, nose, mouth, and throat), lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, lungs, abdomen and a brief examination of the neurological system.

Height will be recorded in centimeters (cm) with the subject's shoes removed. Body weight will be measured in kilograms (kg); subjects will remain in their normal clothing with shoes and jacket (and/or outer clothing) removed.

12.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a brief questionnaire that provides for the identification, quantification and standardized assessment of the occurrences and severity of suicidal ideation and behavior (see http://cssrs.columbia.edu) (Posner 2011). The typical administration time is a few minutes. The "Baseline Version" of the C-SSRS will be assessed at Screening. The C-SSRS "Since Last Visit" version will be assessed at Day -1, Day 36, Day 72, Day 109, and Early Termination.

12.4. Vital Signs

Vital sign measurements will be obtained after the subject has been seated for 3 minutes. Vital signs will include sitting blood pressure (systolic and diastolic measurements), pulse rate (beats per minute), respiratory rate (breaths per minute), and oral temperature. In order to ensure accuracy, out-of-range vital signs may be repeated once, at least 2 minutes after an abnormal finding.

Vital signs will be collected at prior to the first dose/application and weekly thereafter. Temperature checks may be permitted daily.

12.5. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be obtained after the subject has been in a supine position for a minimum of 3 minutes. Abnormal ECGs may be repeated for confirmation in which case only

the repeated ECG will be recorded. The QT interval corrected for heart rate will be calculated with Fridericia's formula (QTcF).

ECGs will be obtained at Screening, Day -1, ET and EOS visit.

12.6. Clinical Laboratory Measurements

All clinical laboratory samples will be sent to a local laboratory for analysis. Up to approximately 40 mL of blood will be collected for clinical chemistries, hematology, and pregnancy test (if applicable) from each subject during the study. During the Screening Period, Clinical Laboratory Measurements may be repeated at the discretion of the Investigator.

The Clinical Laboratory evaluations will consist of the following:

- Total Hematology as well as differential and Coagulation: red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), hemoglobin, hematocrit and platelets, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT).

- Serum Chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase, bicarbonate, total bilirubin, blood urea nitrogen, phosphorus (inorganic) calcium, chloride, creatine phosphokinase, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, total protein, and uric acid.

- Urinalysis: microanalysis for specific gravity, pH, protein, glucose, ketones, blood, nitrites, leukocytes. If positive for blood, protein or nitrites, a microscopic examination will be performed.

- Serology: hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus antibody.

- Pregnancy Tests: will be performed for all female subjects. A serum β-hCG pregnancy test will be performed at Screening. A urine pregnancy test will be performed at check-in, Day 36, Day 72, Day 109, and the Early Termination visit,. A positive pregnancy test will exclude a subject from enrollment into the study. A positive urine pregnancy test will be confirmed with a serum β-hCG pregnancy test.

- Urine Screen for Alcohol, Drugs of Abuse: Urine samples will be tested for alcohol, drugs of abuse (amphetamines, methamphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and opioids) at Screening and at check-in of the Treatment Phase. If the test is positive for any of the tested analytes the subject will be excluded from further study participation.

- Laboratory safety tests will be obtained at the Screening visit, Day -1, Day 36, Day 72, Day 109, and at the Early Termination visit. In addition, laboratory safety tests may be performed at various unscheduled time points if deemed necessary by the investigator.

12.7. COVID-19 Testing

Subjects must have a negative COVID-19 viral test at Screening and Day -1 in order to be eligible for enrollment. COVID-19 testing will be performed weekly while subjects are housed in the clinic. Other reasons for testing could include but are not limited to:

- If a subject displays COVID-19 symptoms (fever, cough, loss of taste or smell, or diarrhea).
- If any subject is suspected of coming in contact with a confirmed COVID-19 positive person.
- At the discretion of the Principle Investigator/in consultation with the Medical Monitor.

A detailed site COVID-19 Continuity Plan could be provided to include guidance for testing frequency and related safety precautions.

12.8. Adverse Event Assessments

Adverse events (AEs) shall be monitored continuously from the administration of the first dose of study drug until either the Follow-Up or Early Termination visits as noted on the Schedule of Events. AEs will be monitored continuously and solicited using a non-leading question immediately after dosing and at 1, 3, 5, 10, 24 hours post-dose, after all other procedures at each specified time are performed. Definitions and details of AE reporting and documentation are listed in **Section 19**.

13. PHARMACOKINETIC ASSESSMENTS

13.1. Pharmacokinetic Plasma Sample Collection

Pharmacokinetic Sampling for Treatments A and B (TDS application):

The blood PK samples will be collected at the nominal time points listed below ±5 minutes for the first 24 hours and 10 minutes thereafter.

The following blood PK samples will be collected in 2 mL EDTA K2 lavender top tubes:

- Week 1 (Days 1 to 7): Pre-TDS #1 application (Day 1), and at 2, 6, 12, 24, 48, 72, 96, 120, and 144 h after TDS #1 application.
- Week 2 (Days 8 to 14): Pre-TDS #2 application (Day 8 at 168 h after TDS #1 application), and at 24, 48, 72, 96, 120, and 144 h after TDS #2 application.
- Week 3 (Day 15 to 21): Pre-TDS #3 application (Day 15 at 168 h after TDS #2 application).
- Week 4 (Day 22 to 28): Pre-TDS #4 application (Day 22 at 168 h after TDS #3

application).

The following blood PK samples will be collected in 4 mL EDTA K2 lavender top tubes:

- Week 5 (Day 29 to 35): Pre-TDS #5 application (Day 29 at 168 h after TDS #4 application), and at 3, 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156 h after TDS #5 application
- Week 6 (Day 36): Pre-TDS #5 removal (Day 36 at 168 h after TDS #5 application), and at 2, 6, 8, 10, and 12 h after TDS #5 removal.

The 168-h post-dose PK blood samples will be collected before removal of the worn TDS.

Pharmacokinetic Sampling for Treatment C (oral dosing):

The blood PK samples will be collected at the nominal time points listed below ±5 minutes for the first 24 hours and 10 minutes thereafter.

The following blood PK samples will be collected in 2 mL EDTA K2 lavender top tubes:

- Week 1, Day 1: Pre-Dose, and at 1, 2, 3, 4, 6, 8, 12 and 24 h after oral administration (before Day 2 oral administration)
- Week 2: Day 8 Pre-Dose
- Week 3: Day 15 Pre-Dose
- Week 4: Day 22 Pre-Dose

The following blood PK samples will be collected in 4 mL EDTA K2 lavender top tubes:

- Week 5: Day 29 Pre-Dose
- Week 5: Day 35 Pre-Dose, and 1, 2, 3, 4, 6, 8, 12 and 24 h after oral administration (the 24-h sample will be collected on Day 36.

One hundred and four (104) blood samples will be collected during the entire treatment period. A total of approximately 316 mL blood per subject will be drawn for PK analysis.

Detailed instructions for the collection, processing, storage and shipment of the plasma PK samples will be included in the Laboratory Manual. The date and time of collection of each PK sample will be recorded.

13.2. Pharmacokinetic Sample Shipment

The plasma samples will be transferred to the analytical laboratory after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. Prior to shipment, the samples will be appropriately packed in a Styrofoam cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 24 hours for local shipments and for at least 48 hours for remote shipments. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of patients, and number of samples included in the shipment.

All frozen PK samples will be transferred with accompanying documentation to:

13.3. Bioanalytical Methodology

For all subjects, blood samples for the determination of donepezil and 6-O-desmethyl donepezil (active metabolite of donepezil) will be collected in blood collection tubes containing di-potassium ethylenediaminetetraacetic acid (K2EDTA). Following blood collection, samples will be cooled in an ice bath and centrifuged (approximately at 3000 rpm for 7 minutes) under refrigeration at a temperature of approximately 4°C as soon as possible. Within 90 minutes of collection, plasma samples will be divided into 2 aliquots and stored in suitably labeled tubes at -20±10°C, pending assay. At the end of the study, samples will be shipped in separate shipments to the analytical laboratory for analysis. Subsequent shipments will be sent after receipt in good condition of the previous shipment at the analytical laboratory.

A validated LC/MS/MS method will be used determination to determine the content of donepezil and 6-O-desmethyl donepezil in human plasma. The current method is validated for quantitation of donepezil in human plasma over the concentration range of 0.300 ng/mL to 45.0 ng/mL. A bioanalytical method for 6-O-desmethyl donepezil in human plasma will be developed and validated.

13.4. Subjects to Analyze

The PK samples from all subjects will be analyzed.

14. ADHESION ASSESSMENTS AND PATCH PHOTOGRAPHY

Adhesion assessments will be assessed in person by trained CRU staff and assessments of adhesion will be based on the percentage of the total surface area of the TDS that is adhered to the skin. The CRU staff member will record the percentage based upon the actual measurement at each time point with the CRU staff member blinded to the previous recorded percentage. Tactile pressure to the TDS must not be applied during the adhesion determinations A grid overlay with boxes will be used to assist with estimating the % adhesion.

Adhesion Assessments will be performed for Treatment A and B only. Adhesion assessments and photographs will be performed every 12 hours at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168 hour following TDS application and at times that a TDS is removed at or before Early Termination. The 168-hour assessment will be conducted prior to the next TDS application, if applicable. Adhesion assessments will be performed in all periods with TDS applications.

At any time of full detachment of any TDS, the time of full detachment and its 0% adherence will

be recorded, and the 0% adhesion will be assigned to all remaining adhesion time points of the current wear period. No taping of the TDS will be allowed.

At each adhesion assessment time point, a photograph will be taken as evidence of the extent of TDS adhesion to the skin (as support of the visual observation of the adhesion percentage but not to be used for automated or photometric analysis).

Following removal of each TDS, the presence or absence of remaining adhesive residue will also be recorded.

14.1. Patch Detachment

If a TDS partially or fully detaches from the skin, actions to reapply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., taping) must be avoided throughout the study. TDS detachment must not be inappropriately inhibited (e.g., by the constant pressure applied by a person or an object such as the back of a chair).

If a TDS fully detaches from the skin, the TDS must not be reapplied, and no fresh TDS will be applied for the remainder of the intended wear period. The time of full detachment of any TDS and its 0% adherence will be recorded, and the 0% adhesion will be assigned to all remaining adhesion time points of the current wear period.

15. IRRITATION ASSESSMENTS/SKIN TOLERABILITY

Dermal response scores, other effects numerical scores, and the combined skin irritation score (calculated as the sum of the dermal response and other effects scores) will be summarized by post removal time point (0.5, 24, 48, 72 hours post removal). Skin irritation will be followed until skin tolerability scores are ≤1. Separate summaries by treatment and by post removal assessment time point will be provided. Whole number scores will be used. When evaluating a dermal response, at least 25% or more of the patch area should demonstrate an observable response. When multiple observable dermal responses are present, each observable response shall represent at least 25% or more of the patch area. It is recommended when determining the percentage of patch area with an observable response, record each dermal response and determine if each one response represents at least 25% or more of the patch area.

Skin tolerability assessments will be performed prior to the TDS application and after removal of the TDS application during each period using the following scale:

15.1. Tolerability Scales (Dermal Response and Other Effects)

Skin Appearance	Score
No evidence of irritation	0

Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site	7

Other Effects

Observation	**Score (Numerical Equivalent)**
Slightly glazed appearance	A (0)
Markedly glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the TDS site	G (3)
Small petechial erosions and/or scabs	H (3)

Source: FDA Draft Guidance: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs. 2018.

16. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

16.1. Withdrawal of Subjects from the Study

A subject may be discontinued or choose to withdraw from study treatment at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent.

- Subject is not compliant with study procedures.
- Adverse event that in the opinion of the Investigator would be in the best interest of the subject to discontinue study treatment.
- Protocol violation requiring discontinuation of study treatment.
- Lost to follow-up.
- Sponsor request for early termination of the study.
- Positive pregnancy test (females).
- Out-of-range vital signs, at the discretion of the Investigator. In order to ensure accuracy, out-of-range vital signs may be repeated once, at least 2 minutes after an abnormal finding.
- For other reasons (e.g., Investigator/Sponsor request, inappropriate behavior, social reasons).

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

16.2. Withdrawal of Subjects Post-Dose Study Drug

If a subject meets withdrawal criteria post-dose during the Treatment Phase, the subject will complete, if possible, all study procedures after the current (last) administration of study drug (including PK sample collections) before starting Early Termination procedures. The subject will be withdrawn and Early Termination procedures will be completed prior to the subject's discharge from the clinic.

At the discretion of the Investigator, ensuring the safety of the subjects, any ET procedures that were already performed on the same day as part of the procedures of the current treatment phase, do not need to be repeated.

The Sponsor may be contacted if clarification is required on a case-by-case basis.

16.3. Replacement of Subjects

Treated subjects who discontinue treatment or withdraw early from the study will not be replaced.

17. STATISTICAL METHODS

More details of the statistical analyses will be defined in the Statistical Analysis Plan (SAP). Prior to the analysis of the final study data, a detailed SAP will be written describing all analyses that will be performed.

17.1. Analysis Populations

There are 5 populations in this study:

Randomized Population: all subjects who signed the informed consent form and are assigned a randomization number on Day 1 of Treatment Period 1, prior to the first dose of study drug.

Intent-to-Treat (ITT) Population: all randomized subjects who take a least 1 dose of study drug. Demographics and baseline characteristics will be summarized for the ITT population.

Pharmacokinetic Per-Protocol (PK-PP) Population: all ITT subjects for a particular treatment without any major protocol deviations that could affect the pharmacokinetic endpoint for that particular treatment, who received adequate treatment to reach steady state for donepezil in the particular treatment (for example, adequate TDS wear), and who provide the plasma concentrations required to calculate the donepezil $AUC_{0\text{-}168,SS}$ after a particular treatment. Detailed criteria for the PK-PP Population will be listed in the SAP. Demographics and baseline characteristics will be summarized for the PK-PP Population by treatment. Data from the PK-PP Population will be used for PK data listings, with descriptive statistics, and for statistical comparison between the treatments in the Test Products and the Reference.

Safety Population: all randomized subjects who receive at least one dose of study drug and who have at least one safety assessment. Safety measures will be analyzed for all subjects in the Safety Population.

Adhesion Per-Protocol (ADH-PP) Population: The ADH-PP population will be based on the number of TDSs applied (instead of the number of subjects). All TDSs applied will be part of the ADH-PP Population except those that were intentionally removed early in the trial (e.g., because of unacceptable irritation) or from subjects who discontinued use of a TDS before the end of the 7-day wear period for reasons unrelated to adhesion (e.g., because of a protocol violation or an adverse event). Individual case reports describing any subjects/TDS who were excluded from the ADH-PP Population, and the reasons for their exclusion, will be included in the clinical study report. The ADH-PP Population will be used for the summaries and statistics of adhesion data.

17.2. Determination of Sample Size

An adequate number of subjects (approximately 60 subjects) will be enrolled in the study to plan for 48 subjects to complete all study periods. This sample size was based on results of a previous steady-state study comparing 10 mg/day donepezil TDS to oral 10 mg/day donepezil (Study CL-P-15086) that showed an AUC geometric mean ratio of 1.04 and a coefficient of variation of 29.3%. The calculated sample size of 48 subjects is estimated to show at least 90% power to assess bioequivalence within the limits of 80 to 125% for the geometric mean ratio if the true expected geometric mean ratio is 1.05 (assuming a coefficient of variation of 29%) for AUC.

Based on adhesion scores from previous studies with the donepezil TDS, the planned sample size of the current study should be more than adequate to demonstrate, based on a one-sided lower 95% confidence interval created with 80% power, that >80% of patches are adhered for at least 75% throughout the wear period.

17.3. Pharmacokinetic Analysis

17.3.1. Pharmacokinetic Parameters

PK parameters will be calculated for the PP population from plasma concentrations of donepezil and 6-O-desmethyl donepezil (active metabolite) using standard, non-compartmental methods using Phoenix® WinNonlin® (Version 8.3 or higher, Certara USA, Inc., Princeton, NJ). Pharmacokinetic parameters at steady state (Week 5) will include $AUC_{0\text{-}24,SS}$ (daily AUC), $AUC_{0\text{-}168,SS}$, T_{lag}, C_{max}, C_{min}, C_{avg}, C_{trough}, C_{tau}, percent peak-to-trough fluctuation (FLUCP). After oral administration, $AUC_{0\text{-}24,SS}$ will be calculated and multiplied by 7 to obtain $AUC_{0\text{-}168,SS}$. In some subjects, because of the lag time, the Cmax and Tmax values at steady state may be observed after removal of the TDS (past 168 hours after TDS application). Additional PK parameters will be reported (see SAP for details).

Area under the plasma concentration versus time curve will be calculated by the linear trapezoidal rule. Concentrations that are below the limit of quantification (BLQ) will be treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations will be treated as zero from time zero up to the time at which the first quantifiable concentration is observed; embedded and/or terminal BLQ concentrations will be treated as “missing.

17.3.2. Descriptive Statistics for Pharmacokinetics

For the plasma concentrations at each time point and for each PK parameter, parametric and nonparametric descriptive statistics will be calculated. Parametric descriptive statistics include number of subjects (n), arithmetic mean and standard deviation (SD), and percent coefficient of variation (%CV). Nonparametric descriptive statistics include minimum, Q1 (25th percentile), median, Q3 (75th percentile), and maximum. Individual plasma concentrations and PK parameters and descriptive statistics by treatment will be listed.

PK parameters of exposure (concentrations and AUCs) after the 5 mg/day TDS application will be multiplied by 2 to adjust for the lower dose (dose-normalization) before comparison to the 10 mg/day treatments.

17.3.3. Plasma Concentration-Time Plots

Individual subject and mean plasma concentration-time profiles will be plotted for donepezil by treatment on linear and logarithmic concentration axes.

17.3.4. Statistical PK Comparison between Treatments

Statistical comparison of the PK parameters of exposure ($AUC_{0-24,SS}$, $AUC_{0-168,SS}$, C_{max}, C_{min}, C_{tau}, percent peak-to-trough fluctuation (FLUCP).) at steady state for donepezil among the 3 treatments will be performed using an Analysis of Variance (ANOVA) model for a 3-way crossover design on the ln-transformed data with sequence, period and treatment as the fixed effects and subject within sequence as a random effect. A statistically significant difference is defined as $p < 0.05$. Intersubject, intrasubject and total variability (coefficient of variation in percent, CV%) of the PK parameters will be reported.

PK parameters of exposure (concentrations and AUCs) after the 5 mg/day TDS application will be multiplied by 2 to adjust for the lower dose (dose-normalization) before statistical comparison to the 10 mg/day treatments.

17.3.5. Time to Steady State Assessment

Assessment of time to achieve steady-state will be performed by a review of weekly donepezil trough levels (C_{tau}) at time points immediately prior to dosing on Days 15, 22, 29, and 36 in each treatment period. The univariate analysis method described by Chow and Liu for examining when steady-state is attained will be implemented using log-transformed trough plasma concentrations. Modifications to the method for Treatment Periods 2 and 3 will be explained in the SAP, to possibly adjust for the attainment of a new steady state after switching to a new treatment without a washout period after the previous treatment.

17.3.6. Statistical Assessment of Relative Bioavailability

To examine the relative bioavailability at steady state of the 5 and 10 mg/day TDS (Tests) relative to oral donepezil (Reference), plasma donepezil exposure as characterized by $AUC_{0-168,SS}$ will be assessed and compared utilizing bioequivalence criteria. The least squares geometric means (LSGM) of the PK parameters for each treatment will be reported. Point estimates and 90% Confidence Intervals (CI) for the Test to Reference ratios of geometric means will be provided. Similar bioavailability for donepezil will be concluded if the 90% CIs of the LSGMs lie within the acceptable range of 0.80 to 1.25 for $AUC_{0-168,SS}$. Forest plots presenting the point estimate and 90% confidence intervals for $AUC_{0-168,SS}$ will be constructed for the comparisons between the 5 mg/day and 10 mg/day donepezil TDS applications (Tests) and oral Aricept® (Reference).

Since the intention of the patch is to decrease the peak-to-through fluctuations with lower Cmax after the patch application compared to daily oral Aricept dosing, rather than using the conventional bioequivalence criterion for C_{max}, it is stipulated that mean steady-state donepezil C_{max} after patch administration should remain between the steady-state C_{max} and C_{min} after daily oral Aricept® administration.

17.4. Adhesion Analysis

TDS adhesion score results (percentage adhesion) for each TDS strength will be summarized separately for Weeks 1 through 5 and across all wear periods (Weeks 1-5 combined) as follows:

- Summary statistics (mean, SD, minimum, Q1, median, Q3, maximum) for the mean adhesion score, where the mean adhesion score for each patch is the average of the patch adhesion scores across the entire wear period.
- Adhesion score distribution at each adhesion measurement time point post patch application (i.e., 12, 24, …, and 168 hours).
- Average adhesion score at each adhesion measurement time point post patch application.
- Number (%) of patches that are completely detached during the 7-day wear period.
- Number (%) of patches with adhesion <50% at any adhesion measurement time point during the 7-day wear period.
- Summary of frequency of time a patch was first observed with adhesion <50% during the 7-day wear period.
- Number (%) of patches with adhesion ≥75% at all adhesion assessment time points during the 7-day wear period

To assess whether at least 80% of the TDS applied are at least 75% adhered throughout the 7-day wear period, a one-sided 95% confidence interval will be determined for the probability (p) that a randomly selected TDS maintains at least 75% adhesion throughout the entire wear period. If the 95% lower confidence limit for p is greater than 80%, acceptable TDS adhesion will be concluded. The method for the calculation of the 95% lower confidence limit and the justification of the method will be provided in the SAP.

To calculate the mean adhesion score and associated statistics, the lowest adhesion score at each time point after the baseline time point (t_0) will be carried forward to subsequent time points until a lower score is observed.

17.5. Subject Disposition and Demographic/Baseline Characteristics

The numbers of subjects screened, the number of subjects randomized overall (Randomized Population) and per treatment sequence group, and the number of subjects in the ITT and PP populations overall and by treatment sequence group will be listed. Differences between the number of subjects in the analysis populations will be explained. For randomized subjects who discontinue from the study, the primary reason for discontinuation will be listed and summarized by treatment after which they discontinued.

Summary statistics will be provided by treatment sequence and overall for demographic characteristics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, BMI) in the ITT and PP populations. Demographic data and baseline characteristics will be

compared among treatment sequence groups for the ITT and PP population.

17.6. Safety Analysis

All analyses of safety will be conducted on the Safety Population. The safety assessment will be based on adverse events, physical exams, vital signs, ECG parameters, C-SSRS, safety laboratory tests, and irritation scores (for treatments with TDS).

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with new onset during the study between the initiation of study drug and 5 days after the last dose of study drug will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of serious adverse events, and adverse events leading to early discontinuation from the study will be presented through data listings.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those subjects with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings.

17.7. Interim Analysis

No interim analysis is planned for this study.

18. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

18.1. Adverse Events

18.1.1. Recording and Monitoring of Adverse Events

For the purpose of this clinical trial, all Adverse Events will be recorded and monitored for all enrolled subjects from the moment they receive the dose of study drug until they complete the study at the EOS (the Follow-Up visit or the Early Termination Visit).

18.1.2. Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator or designee will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

18.1.3. AE Grading

The severity of each AE will be graded by the investigator using the following categories:

Mild	Does not interfere with subject's usual function (awareness of symptoms or signs, but easily tolerated [no specific medical intervention required]).
Moderate	Interferes to some extent with subject's usual function (enough discomfort to interfere with usual activity [minimal intervention; local intervention; noninvasive intervention]).
Severe	Interferes significantly with subject's usual function (incapacity to work or to do usual activities [significant symptoms requiring hospitalization or invasive intervention]).

If there is a change in severity of an AE, only the maximum severity of the AE should be recorded.

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

- None
- Study product stopped
- Study product temporarily interrupted
- Concomitant medication
- Other, specify

18.1.4. AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following:

1. Definitely - Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage

of the drug; and that is not explained by any other reasonable hypothesis.

2. Probably - An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.

3. Possibly - An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.

4. Unrelated - An event that can be determined with certainty to have no relationship to the study drug.

18.2. Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

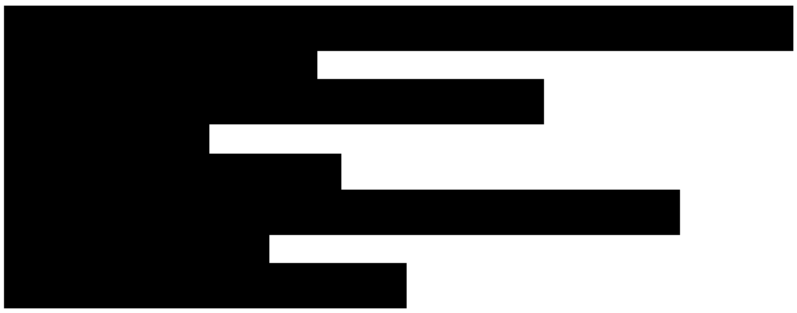
Note that AEs of Grade 3 due to hospitalization or prolongation of a hospitalization, and Grade 4 and Grade 5 per CTCAE grading criteria are classified as SAEs.

18.2.1. Serious Adverse Event Reporting

Within 24 hours after a SAE detection, observation, or report of occurrence (regardless of the relationship to test article), the Investigator or designee will enter the SAE into the electronic database. The investigator/qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to the appropriate sponsor contact. If the EDC system is temporarily unavailable, the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to the appropriate sponsor contact. Upon return of the availability of EDC

system, the SAE information must be entered into the eCRF.

The contact information for SAE reporting is provided below:



These SAE reports must contain the following information:

1. Study name/number
2. Study Drug
3. Investigator details (name, phone, fax, e-mail)
4. Subject Number
5. Subject Demographics
6. Clinical Event
7. Description
    a. Date of onset
    b. Treatment (drug, dose, dosage form)
    c. AE Relationship to study drug
    d. Action taken regarding study drug in direct relationship to the AE
    e. Criteria for "Serious" applicable to the AE
8. Cause of death (whether or not the death was related to study drug)
9. Autopsy findings (if available)

Any SAE that occurs during the study should be recorded by the clinical site and reported to the CRO. The CRO will notify the Sponsor by the end of the next business day after SAE notification receipt from the site.

SAEs considered, probably, or possibly related to study drug shall also be classified by the Sponsor as being "expected" or "unexpected." An unexpected event is one that is not listed in the Investigator's Brochure.

The person responsible for the study shall ensure the study has been carried out in accordance with local pharmacovigilance regulations.

All serious event reporting by Sponsor will adhere to 21 CFR 312.32 for IND drugs (7-day or 15-day alerts) and 21 CFR 314.80 for marketed drugs (15-day alerts). Unexpected fatal or life threatening SAEs considered related to the study drug should be reported to the FDA by the Sponsor with an IND Safety report within 7 days. The Institutional Review Board (IRB) will be notified of

the alert reports per FDA regulations.

18.3. Adverse Event Treatment and Follow-up

All AEs, including SAEs, will be followed to resolution when possible. All AEs and treatment administered will be recorded on the case report form (eCRF). Treatment may be rendered on site under the direction of the Investigator as appropriate. Events requiring diagnostic evaluation or treatment beyond the scope of what is available and appropriate within the clinical research unit shall be referred in a timely basis to other care providers. Records of diagnostic and therapeutic interventions shall be requested in compliance with HIPAA requirements, and those received shall be retained in the subject's file.

SAE assessment, treatment, and follow up shall be performed up to at least 30 days after last dose for events considered definitely, probably, or possibly related to study drug, and continue until resolved or clinically stable.

19. PREGNANCY

Females with a positive pregnancy test will terminate the study early (**Section 10.5**). The initial report of a pregnancy during the study will be provided to the sponsor within 24 hours of the incident identification and to the IRB within a time frame after the incident identification as required by the IRB.

All pregnancies will be followed to at least the completion/termination of the pregnancy. The Investigator will document the subject visits accordingly and record the information in the clinical site's source documents. If the pregnancy continues to delivery, the outcome (health of the infant), in addition to the maternal health status, must be included in the report.

Pregnancy will not be considered an AE or SAE; any pregnancy complication or termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

20. PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, Investigator, or Sponsor fails to adhere to significant protocol requirements that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare. Examples of protocol violations may include the following:

1. Inadequate or delinquent Informed Consent
2. Inclusion/exclusion criteria not met
3. Unreported serious adverse events
4. Multiple visits missed or outside permissible windows
5. Materially inadequate record keeping
6. Intentional deviation from protocol, Good Clinical Practice, or regulations by study

personnel
7. Subject repeated non-compliance with study requirements

It is the Investigator's responsibility to report to the IRB of any Protocol Violation(s) according to the IRBs policy. Copy of the IRB submission will be filed in the site's regulatory binder and in the Sponsor's files.

21. DATA MANAGEMENT AND RECORD KEEPING

21.1. Data Management

Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed and dated. A CRF must be completed for each participant who has given informed consent. The CRFs and source documents must be made available to Sponsor and/or its representatives.

21.2. Record Keeping

The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, subject source data (including records of subjects, subject visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae.

The Investigator and affiliated Institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated Institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

21.3. Access to Source Data/Documents

The Investigator and research Institution agree that the Sponsor, their representatives, the IRB, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

22. QUALITY CONTROL AND QUALITY ASSURANCE

By signing the protocol, the Institution and the Sponsor agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in

compliance with the protocol, accepted standards of Good Clinical Practice. (GCP), ICH and other applicable regulations.

23. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In this study, the 2008 version of the Declaration of Helsinki will be adhered to. It can be found on the website of The World Medical Association: http://www.wma.net/en/30publications/10policies/b3/17c.pdf

24. PUBLICATION POLICY

Confidentiality, presentation, and publication of manuscripts containing the study data, and patent applications related to unpublished study-related information and unpublished information given to the Investigator by the Sponsor and/or its representatives shall be handled as set forth in a mutual written agreement between the Sponsor and the Institution. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

25. FINANCING AND INSURANCE

25.1. Finances

Prior to starting the study, the Principal Investigator and/or Institution will sign an agreement with the Sponsor related to conducting the clinical trial. This agreement will include the financial information agreed upon by the parties.

25.2. Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the other collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the IRB according to regulatory requirements.

26. COMPLETION OF STUDY

The end of the study will be at the time of the last subject, last visit. The IRB will be notified about the end of the study according to regulatory requirements.

27. STUDY ADMINISTRATIVE INFORMATION

27.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the Investigator by the Sponsor. All substantial protocol amendments will undergo the same review and approval process as the original protocol and may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB according to all relevant regulatory requirements.

A protocol amendment is considered to be a substantial amendment if it is likely to affect the safety, physical, or mental integrity of subjects in the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any Investigational Medicinal Product used in the study.

Any other minor changes to the protocol not considered to be substantial amendments will not need prior approval of the IRB and will be communicated to the Investigator by the Sponsor.

28. REFERENCES

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