Statistical Analysis Plan

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

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1 INTRODUCTION

This document details the planned statistical analyses for the *Corium, Inc.*, protocol "*CL-P-20003*" study titled "*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*".

The proposed analyses are based on the contents of the final version of the protocol (dated *2-OCT-2020*), the protocol amendment #1 *(dated 26-OCT-2020)*, and the protocol clarification memo #1 (*dated 30-OCT-2020*).

This is a Phase 1, open-label, randomized, 3-period, 3-treatment, 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 potential for continued drug absorption after TDS removal, an additional non-treated PK sampling 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) to evaluate the presence of this phenomenon. These samples at the very beginning of the terminal phase will not be used for any terminal-phase assessments due to their truncated nature.

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:** 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).

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.

2 STUDY OBJECTIVES

2.1 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®.

2.2 Secondary Objective

- 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.

2.3 Safety Objective

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

3 ENDPOINTS

3.1 Primary Endpoints

- Primary pharmacokinetic parameters at steady state (Week 5) calculated for plasma concentrations of donepezil will include: $AUC_{0\text{-}168,ss}$ and $C_{max,ss}$

3.2 Secondary Endpoints

- Secondary pharmacokinetic parameters on Week 1 after the first TDS application calculated for plasma concentrations of donepezil will include: $AUC_{0\text{-}168}$, $AUC_{0\text{-}24}$ (daily AUC), C_{max}, T_{max}, and T_{lag}.
- Secondary pharmacokinetic parameters at steady state (Week 5) calculated for plasma concentrations of donepezil will include: $AUC_{0\text{-}24,ss}$ (daily AUC), T_{lag}, $T_{max,ss}$; $C_{min,ss}$; $T_{min,ss}$; $C_{avg,ss}$; C_{trough}; and percent peak-to-trough fluctuation (FLUCP).
- Trough donepezil levels (C_{tau}) reported at the end of each dosing interval (taken predose on Days 8, 15, 22, 29, and 36 after TDS treatments and on Days 8, 15, 22, 29, and 35 after Aricept oral treatment)
- Skin adhesion assessments for each TDS will be evaluated every 12 hours during wear as the percentage of the total surface area that is adhered to the skin, assessed in person by trained observers.
- All PK parameters and trough levels for 6-O-desmethyl donepezil (active metabolite)

3.3 Safety Endpoints

- Adverse events (AEs), physical examinations, vital signs assessments, clinical laboratory evaluations, C-SSRS evaluations, electrocardiograms (ECGs), and skin tolerability assessments

4 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 $AUC_{0\text{-}168,ss}$ 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 $AUC_{0\text{-}168,ss}$.

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.

5 RANDOMIZATION

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. This is an open-label study. Study treatments will not be blinded.

6 PLANNED ANALYSES

The final clinical study report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Populations

Subjects excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2.

6.1.1 Randomized Population

The Randomized Population includes 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.

6.1.2 Pharmacokinetic (PK) Population

The PK Population includes all subjects without major protocol deviations that could affect pharmacokinetics and who have at least one PK parameter derived. Subjects that are withdrawn from the study prior to study completion (early termination, ET) will be excluded from the PK population for the period during which ET occurred. Additionally, subjects with 100% patch detachment occurring in Weeks 3, 4, or 5 will be excluded from the PK population and subsequent analyses. The PK population will be used in the PK analysis and to generate summary statistics for PK endpoints.

6.1.3 Relative Bioavailability (BA) Population

The Relative Bioavailability Population includes all PK Population subjects that have $AUC_{0\text{-}168,ss}$ and/or $C_{max,ss}$ for TDS 10 mg and Aricept treatments.

Demographics and baseline characteristics will be summarized for the Relative Bioavailability Population by treatment. Data from the PK Population will be used for PK parameter data listings, with descriptive statistics. Statistical comparison of the test and reference products will be based on the Relative Bioavailability Population.

All protocol deviations will be assessed and documented on a case-by-case basis before database lock, and deviations considered to have a potentially serious impact on the PK results will lead to the relevant subject being excluded from the Relative Bioavailability Population. Before database lock, potential subject exclusions from the PK and Relative Bioavailability Populations will be reviewed by the Sponsor and documented in a subject evaluability document.

6.1.4 Safety Analysis Population

The Safety Analysis Population includes 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 Analysis Population.

6.1.5 Skin Irritation Population

The skin irritation population includes all TDSs except those removed prior to the end of the 7-day wear period (e.g., dropouts) for reasons unrelated to skin tolerability, or those that became detached due to lack of adhesion. TDSs that are removed due to irritation or other skin effects will be retained in the Skin Irritation Population. The Skin Irritation Population will be used for summaries of skin irritation data.

6.1.6 Adhesion Population

The Adhesion Population will be based on the TDS patches (instead of subjects). All TDSs applied will be part of the Adhesion Population except those that removed before the end of the 7-day wear period for reasons unrelated to adhesion (e.g., due to unacceptable skin irritation, because of a protocol violation, an adverse event, or subject dropout). Individual subject case reports for any subject with a TDS excluded from the Adhesion Population, and the reasons for the TDS's exclusion, will be included in the clinical study report. TDSs that became detached for reasons related to adhesion will not be excluded from the Adhesion Population. The Adhesion Population will be used for the summaries and statistics of adhesion data.

Demographics and baseline characteristics will be summarized for the Safety Analysis Population by treatment. Data from the PK Population will be used for PK data tables with descriptive statistics by treatment. Data from the Relative Bioavailability Population will be used for statistical comparisons between TDS 10 mg and Aricept treatments.

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered to have a serious impact on the efficacy results will lead to the relevant subject being excluded from the PK and Relative Bioavailability Populations. Prior to database lock, blinded adhesion data will be reviewed by the Sponsor and pharmacokinetics to identify any potential subject exclusions from the PK and Relative Bioavailability Populations.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

For variables that will be summarized by treatment, the baseline for each period is defined as the last non-missing value (either scheduled, unscheduled or repeat) that is collected before dosing, in the relevant period.

6.2.3 Early Terminations Assessments

Early Termination (ET) from the study is defined as withdrawal during the Treatment Phase after a Donepezil TDS has been applied.

ET assessments will be summarized alongside the Follow-Up assessments as the End of Study (EoS) visit.

6.2.4 Study Day

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1

6.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an AE start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing.

All dates presented in the individual subject listings will be as recorded on the eCRF.

6.2.6 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.7 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated. Post-baseline repeat/unscheduled assessments will not be included in summary statistics. However, these repeat/unscheduled post-baseline assessments will be included in the relevant listings.

6.2.8 TDS Adhesion Assessment Scale

TDS adhesion will be assessed every 12 hours (h) after application throughout the wear period. Each time point will be assessed in person by a trained observer based on the percentage of total surface area of skin attachment.

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.

6.2.9 Skin Irritation Assessment Scale

Skin irritation at the patch site will be assessed prior to each TDS application and following TDS removal at 0.5, 24, 48, and 72 h. If the score is greater than 1 at 72 h post-removal, assessments will continue until a score < 1 is reported.

Application sites will be graded using the following two scales:

- an 8-point categorical Dermal Response Scale (see Table 6.2.9.1 below)

  Table 6.2.9.1 Dermal Response Scale

Skin Appearance	**Numeric Score**
No evidence of irritation	0
Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal edema or minimal popular response What was present: • Definite Erythema • Minimal Edema • Minimal Papular Response	2
Erythema and Papules What was present: • Erythema • Papules	3
Definite Edema	4
Erythema, edema, and papules What was present: • Erythema • Edema • Papules	5
Vesicular Eruption	6
Strong reaction spreading beyond the application site	7

- a 6-point categorical Other Effects Scale (see Table 6.2.9.2 below). site will be assessed for skin irritation

  Table 6.2.9.2 Other Effects Scale

Observation	Score (Numeric Equivalent)
No other effects observed	None (0)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudate covering all or part of the TDS site	G (3)
Small petechial erosions and/or scabs What was present: • Small petechial erosions • Scabs	H (3)

Combined scores will be calculated as:
$Combined\ Skin\ Irritation\ Score = (Dermal\ Response\ Score) + (Other\ Effects\ Score)$

Only whole number scores will be used.

6.2.10 Columbia-Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) is a brief questionnaire that provides for the identification, quantification, and standardized assessment of the occurrence and severity of suicidal ideation and behavior (see http://cssrs.columbia.edu) (Posner 2011). The "Baseline" version of the C-SSRS will be assessed at Screening. The C-SSRS "Since Last Visit" version will be assessed on all other study days [Day -1 and End of Treatment (EoT)/ET visit].

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent

Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non fatal)
Category 10	Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome which also has a binary outcome (yes/no).
Composite endpoints based on the above categories are defined below:

- Suicidal Ideation since baseline – A "yes" answer at any time during treatment phase to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.
- Suicidal Behavior since baseline – A "yes" answer at any time during treatment phase to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS.

There will be no imputation of missing data for C-SSRS.

6.2.11 PK Parameters

6.2.11.1 Concentration-Time Data

Blood samples will be collected for plasma donepezil and 6-O-desmethyl donepezil (active metabolite) concentration assessments at the following timepoints (please note, "Day" refers to the day relative to Week 1 dosing in each study period):

Treatments A and B (patch applications):

- 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).
- 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 170, 174, 176, 178, and 180 h after TDS #5 removal

Treatment C (oral dosing):

- Week 1, Day 1: Pre-Dose
- Week 2: Day 8 Pre-Dose
- Week 3: Day 15 Pre-Dose
- Week 4: Day 22 Pre-Dose
- Week 5: Day 29 Pre-Dose
- Week 6: 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).

Concentration-time data prior to Week 5 will be presented by week and nominal time relative to the time of TDS application for that particular week.

For PK analysis and presentation of concentration-time data on Week 5, nominal and actual times will be expressed relative to the time of TDS # 5 application (beginning on Day 29): 0, 3, 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168 (prior to patch removal), 170, 176, 174, 178, and 180 h.

Concentrations that are below the limit of quantification (BLQ) will be treated as zero in the data summarization and descriptive statistics. Individual plasma concentration-time data of donepezil and 6-O-desmethyl donepezil will be plotted on both linear concentration scales and on logarithmic (log10) concentration (semi-log) scales. Mean plasma concentration-time data will be presented by nominal times. For summarizing concentration and linear plots of individual time-concentration profiles, BLQ values will be set to 0. For semi-logarithmic plots of individual concentration-time profiles, BLQ values will be set to missing. Spaghetti plots (all subjects per treatment) and individual plots (comparing treatments for each subject) of the concentration-time data will be presented using actual times on both linear and semi-log scales.

The following plots will be created for donepezil and metabolite 6-O-desmethyl donepezil:

1. Mean concentration-time profiles over the entire collection period (Days 1 through 35) for Treatments A, B, and C (nominal times relative to Day 1, Week 1 dosing)
2. Mean concentration-time profiles for Treatments A, B, and C for Week 5 (Days 29 through 36, predose to 180 h relative to TDS #5 application; Day 35, predose to 24 h for oral dosing)
3. Mean trough concentration-time profiles for Treatments A, B, and C (predose on Days 1, 8, 15, 22, 29, and 36).
4. Spaghetti plots over the entire collection period (Days 1 through 35) for Treatments A, B, and C (actual times relative to Day 1, Week 1 dosing)
5. Spaghetti concentration-time profiles for Treatments A, B, and C for Week 5 (Days 29 through 35, predose to 180 h relative to TDS #5 application; Day 35, predose to 24 h for oral dosing)
6. Spaghetti concentration-time profiles for Treatments A, B, and C for trough concentration-time data (predose on Days 1, 8, 15, 22, 29, and 36)
7. Individual subject concentration-time profiles over the entire collection period (Days 1 through 35) for Treatments A, B, and C (nominal times relative to Day 1, Week 1 dosing)
8. Individual subject concentration-time profiles for Treatments A, B, and C for Week 5 (Days 29 through 35, predose to 180 h relative to TDS #5 application; Day 35, predose to 24 h for oral dosing)
9. Individual subject concentration-time profiles for Treatments A, B, and C for trough concentration-time data (predose on Days 1, 8, 15, 22, 29, and 36)

The PK population will be used to summarize concentration-time data (concentration-time summary tables, mean plots, and individual plots) and for creating concentration-time listings.

6.2.11.2 PK Parameters and Methodology

Concentration-time data for donepezil and active metabolite 6-O-desmethyl donepezil and will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4, Certara, L.P.). PKSO provides protected and structured storage, audit trails, and version control for clinical study data, analyses, and related files, supporting Food and Drug Administration (FDA) 21 CFR Part 11 compliance. The PK population will be used to calculate PK parameters.

In the PK 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”. Actual time relative to TDS #5 application (Days 29 through 35) will be used in the PK analysis. If actual time is missing, nominal (scheduled) time will be used. Actual predose sample times will be set to zero prior to PK analysis.

The following PK parameters will be calculated for Weeks 1 and 5 for donepezil and 6-O-desmethyl donepezil for TDS:

Parameter	Description
Week 1 (Single Dose)	
AUC_{0-24}	The area under the plasma concentration versus time curve, from time zero to 24 h post TDS #1 application, calculated by the linear trapezoidal rule for 24 h intervals within Week 1 (i.e., there will be a total of 7 values for AUC_{0-24} for Day 1 to Day 7 in Week 1) These will be calculated using the partial area function in WinNonlin (ie, AUC_{0-24}, AUC_{24-48}, AUC_{48-72}, AUC_{72-96}, AUC_{96-120}, $AUC_{120-144}$, and $AUC_{144-168}$)
AUC_{0-168}	The area under the plasma concentration versus time curve during a 1 week period (AUC during the wear period for Week 1), calculated by the linear trapezoidal rule.
C_{max}	The maximum observed plasma concentration over a dosage interval following the first TDS application (Week 1)
$T_{max,}$	Time to reach C_{max} after first TDS application on Week 1. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
T_{lag}	Lag time: time for the drug to appear in the systemic circulation after the first TDS application on Week 1
Week 5 (Steady-State)	
AUC_{0-24}	The area under the plasma concentration versus time curve, from time zero to 24 h post TDS #5 application, calculated by the linear trapezoidal rule for 24 h intervals within Week 5 (i.e., there will be a total of 7 values for AUC_{0-24} for Day 1 to Day 7 in Week 5). These will be calculated using the partial area function in WinNonlin (ie, AUC_{0-24}, AUC_{24-48}, AUC_{48-72}, AUC_{72-96}, AUC_{96-120}, $AUC_{120-144}$, and $AUC_{144-168}$)

$AUC_{0\text{-}168,ss}$ (AUC_{tau})	The area under the plasma concentration versus time curve during a 1 week period at steady-state (AUC during the wear period for Week 5), calculated by the linear trapezoidal rule.
$C_{max,ss}$	The maximum observed plasma concentration over a dosage interval at steady-state (Week 5)
$T_{max,ss}$	Time to reach $C_{max,ss}$. If the maximum value occurs at more than one time point, $T_{max,ss}$ is defined as the first time point with this value.
$C_{min,ss}$	Minimum observed non-zero plasma concentration over a dosage interval at steady state (Week 5)
$T_{min,ss}$	The time to reach $C_{min,ss}$ at steady-state (Week 5)
$C_{avg,ss}$	The average plasma concentration over the dosing interval at steady-state (Week 5), calculated as: $C_{avg,ss}=AUC_{tau}/_{tau}$, with $AUC_{tau}=AUC_{0\text{-}168,SS}$ and tau = 168 h
$FLUCP_{ss}$	Percent peak-to-trough fluctuation within the 168 h wear period at steady-state on Week 5, calculated as: $FLUCP=(C_{max,ss}-C_{min,ss})/C_{avg}$ x 100, where $C_{min,ss}$ and $C_{max,ss}$ are obtained between 0 and tau (168 h)
$C_{trough,ss}$	The plasma concentration at the end if the steady-state dosing interval (Day 35)
C_{tau}	The plasma concentration at the end of each dosing interval, taken on Days 8, 15, 22, 29, and 35

The following PK parameters will be calculated for Week 5 for donepezil and 6-O-desmethyl donepezil for orally-administered Aricept:

Parameter	Description
$AUC_{0\text{-}24,ss}$ (AUC_{tau})	The area under the plasma concentration versus time curve at steady-state, from time zero to 24 h after Day 35 administration, calculated by the linear trapezoidal rule.
$AUC_{0\text{-}168,ss}$	The area under the plasma concentration versus time curve at steady-state; this will be estimated by multiplying $AUC_{0\text{-}24,ss}$ on Day 35 by 7.
$C_{max,ss}$	The maximum observed plasma concentration at steady-state on Day 35
$T_{max,ss}$	The time to reach $C_{max,ss}$ on Day 35
$C_{min,ss}$	Minimum observed non-zero plasma concentration over a dosage interval at steady state (Day 35)
$T_{min,ss}$	The to reach $C_{min,ss}$ at steady-state (Day 35)
$C_{avg,ss}$	The average plasma concentration at steady-state on Day 35, calculated as: $C_{avg,ss}=AUC_{tau}/_{tau}$, with tau = 24 h
$FLUCP_{ss}$	Percent peak-to-trough fluctuation on Day 35, calculated as: $FLUCP=(C_{max,ss}-C_{min,ss})/C_{avg,ss}$ x 100, where $C_{min,ss}$ and $C_{max,ss}$ are obtained between 0 and tau (24 h)
$C_{trough,ss}$	The plasma concentration at the end if the steady-state dosing interval (Day 36)
C_{tau}	The plasma concentration at the end of each dosing interval, taken on Days 8, 15, 22, 29, and 36

6.3 Conventions

All safety and clinical data listings, summaries, figures and statistical analyses will be generated using SAS (Version 9.4 or higher)[2].

Summaries of the clinical data will be presented by treatment/sequence and/or overall as depicted in the TFL shells.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.1 or higher) or SAS (Version 9.4 or higher). PK concentration data and PK parameter data will be summarized by analyte and treatment at each nominal sample time.

Treatment labels will be displayed as follows:

Treatment A Treatment B Treatment C

A: 5 mg/day TDS applied weekly, 7-day wear
B: 10 mg/day TDS applied weekly, 7-day wear
C: 10 mg oral Aricept® tablets, QD for 35 days

Treatment sequence labels will be displayed as follows:

Sequence ABC Sequence ACB

Listings will be sorted in the following order treatment sequence (ABC then ACB), subject, treatment, parameter (where applicable), and visit/timepoint (where applicable) unless otherwise stated.

For safety and clinical data continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

PK data (concentration-time data and PK parameter data) will be summarized by the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%), geometric mean, geometric CV%, Q1 (25^{th} percentile), and Q3 (75^{th} percentile). The geometric CV% will be calculated as $100*\text{sqrt}[\exp(\sigma^2)-1]$, where σ^2 was the variance of the log-transformed data. Summaries for PK parameters T_{lag} and $T_{max,ss}$ will not include the geometric mean or geometric CV%.

6.3.1 Decimal Places

Non-PK Data

Decimal places for derived data described in section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

PK Data

Individual donepezil and 6-O-desmethyl donepezil concentrations, PK parameters, and summary statistics will be presented to the precision described in the table below. Time will be presented to 2 decimal places in tables and listings.

Parameter	Individual Values (Table/Listing)	Arithmetic Mean, Geo Mean (Table)	SD (Table)	CV%, Geo CV% (Table)	Median, Max, Min, Q1, Q3 (Table)
Donepezil or 6-O-desmethyl donepezil concentrations	3 sf	2 dp	3 dp	1 dp	3 sf
Time-based parameters (T_{max}, T_{lag}, $T_{max,ss}$, $T_{min,ss}$)[a]	2 dp	3 dp	4 dp	1 dp	2 dp
C_{max}, $C_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, $C_{trough,ss}$, C_{tau}	3 sf	2 dp	3 dp	1 dp	3 sf
AUC parameters (AUC_{0-24}, AUC_{0-168}, $AUC_{0-168,ss}$ $AUC_{0-24,ss}$)	2 dp	3 dp	4 dp	1 dp	2 dp
$FLUCP_{ss}$	3 sf	2 dp	3 dp	1 dp	3 sf

Note: sf=significant figure, dp=decimal place.
[a]Summaries for PK parameters $T_{max,ss}$ and $T_{min,ss}$ will not include the geometric mean or geometric CV%.

Number of subjects (n) will be reported as a whole number. Percent ratios of the geometric least squares means and associated 90% confidence intervals will be reported to 2 decimal places, p-values will be reported to 4 decimal places.

6.4 Subject Disposition

Subject and patch disposition data will be summarized as follows:

- Subject level summaries will include:
  - The number of subjects screened
  - The number of subjects who are in each analysis population will be summarized by treatment sequence and overall for the Randomized Population.
  - The number of subjects who completed the study by treatment sequence for the Randomized Population
  - The number of early terminations, the primary reason for termination will be tabulated by treatment (last treatment received prior to discontinuing from the study) and overall for the Randomized Population.
- Patch level summaries will include:

- The number of patches applied for each treatment
- The number of patches in each population (i.e. Adhesion Population and Skin Irritation Population) by treatment
- The number of patches excluded and the reason for exclusion from each TDS-based population

All subject and patch level disposition data will be listed separately.

6.5 Protocol Deviations

A summary (number, %) of all major and minor protocol deviations will be provided by category reported overall for all subjects. Additionally, a listing of all protocol deviations will be provided within Appendix 16.2.

6.6 Baseline Comparability

Demographics and baseline characteristics will be assessed by treatment sequence and overall in a descriptive manner using the Safety and PK populations, but no formal statistical testing will be performed.

Standard continuous (n, mean, median, SD, Q1 (25^{th} percentile), Q3 (75^{th} percentile) and minimum and maximum values) or categorical variable (number, %) summaries will be presented for the following:

- Demographic data
  - Age at informed consent (IC)
  - Sex – M/F
  - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Mixed Race)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline characteristics
  - Height at Screening (cm)
  - Weight at Screening (kg)
  - Body Mass Index (BMI) at Screening (kg/m^2)
  - Skin type

Individual subject listings of all demographic, medical history, COVID-19 data and baseline characteristics data will be provided.

6.7 Medical History

A complete listing of subject medical history including previous/ongoing conditions and relevant surgical procedures will be presented for the Safety Population.

Medical history data will be coded using the Medical Dictionary of Regulated Activities (MedDRA version 23.1) primary system organ class (SOC) and preferred term (PT).

6.8 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE), version September 2020. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 3) and drug name. If ATC drug class level 3 is not available, then ATC drug class level 2 will be utilized. If ATC drug class levels 3 and 2 are not available, then ATC drug class level 1 will be utilized.

The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented in a subject data listing. The study phase of each medication, determined programmatically based on medication start and end dates, will be presented in the listing. A prior medication is defined as any medication administered prior to the date of the first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

For concomitant medications, the number and percentage of subjects receiving any medication will be summarized as will the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class.

6.9 TDS Application Data

All TDS application and removal data will be listed.

6.10 Statistical Analysis of PK Data

The Relative Bioavailability population will be used in the statistical analyses.

6.10.1 Statistical PK Comparison between Treatments

Statistical comparison of the PK parameters of donepezil and 6-O-desmethyl donepezil exposure (~~$AUC_{0\text{-}24,ss,}$~~ $AUC_{0\text{-}168,ss}$, $C_{max,ss}$, $C_{min,ss}$, $C_{tau,ss}$, $C_{avg,ss}$, and $FLUCP_{,ss}$) at steady-state will be performed using an Analysis of Variance (ANOVA) model for a 2-way crossover design for the comparison of 10 mg TDS vs. Aricept (Treatment B vs. Treatment C) on the ln-transformed data with sequence, period and treatment as the fixed effects and subject within sequence as a random effect. For comparison of 5 mg/day TDS vs. Aricept (Treatment A vs. Treatment C) the analysis will be performed using a ANOVA model with treatment as fixed effect and subject as random effect with Treatment A being dose normalized (PK parameter values multiplied by 2) before the analysis. A statistically significant difference is defined as $p < 0.05$.

Geometric means. inter-subject and intra-subject variability (coefficient of variation in percent, CV_{intra}% and CV_{inter}%, respectively), and intraclass correlation (Chow and Liu, 2009)[4] of the PK parameters will be calculated based on the mixed model results (Proc Mixed of SAS) as indicated below:

[redacted]

Where

[redacted]

[redacted]

```
run;
```

Where

[redacted]

6.10.2 Assessment of Steady-State Achievement

Assessment of time to achieve steady-state for the 3 treatments will be performed by a review of weekly donepezil trough levels (C_{tau}).

In the current study, TDS C_{tau} levels of interest are the plasma concentrations measured immediately prior to TDS removal on Days 8, 15, 22, 29, and 36 . For Aricept, C_{tau} levels of interest are the plasma concentrations measured immediately prior to dosing on Days 8, 15, 22, 29, and 36 following dosing in each period (i.e., Study Days 8, 15, 22, 29, and 36 in Period 1, Study Days 44, 51, 58, 65, 72 in Period 2, and Study Days 80, 87, 94, 101, and 108 in Period 3).

Separate mixed effect models will be used to assess the steady-state of each treatment with consideration of potentially significant sequence effect on Treatments B and C due to lack of washout between periods. For Treatment A the mixed effect model will include Day (Days 8, 15, 22, 29, and 36) as the fixed effect and subject as the random effect. For Treatments B and C two mixed effect models will be used to assess the steady-state:

1. Assess the steady-state of each treatment by period (i.e. Treatment B in Period 2, Treatment B in Period 3, Treatment C in Period 2, and Treatment C in Period 3 using a mixed effect model with Day (Days 8, 15, 22, 29, and 36 in periods 2 or 3) as the fixed effect and subject as the random effect.

2. Assess the steady-state of each treatment combining both periods using a mixed effect model with Day (Days 8, 15, 22, 29, and 36) and sequence as the fixed effects and subject as the random effect.

The least squares means (LSMs) of the log-transformed C_{tau} (pre-dose concentrations) for Treatments A through C will be estimated from the mixed-effect models with Day being treated as a repeated measure within a subject. An unstructured covariance structure will initially be used. If problems with convergence arise, an AR(1) covariance structure will be used.

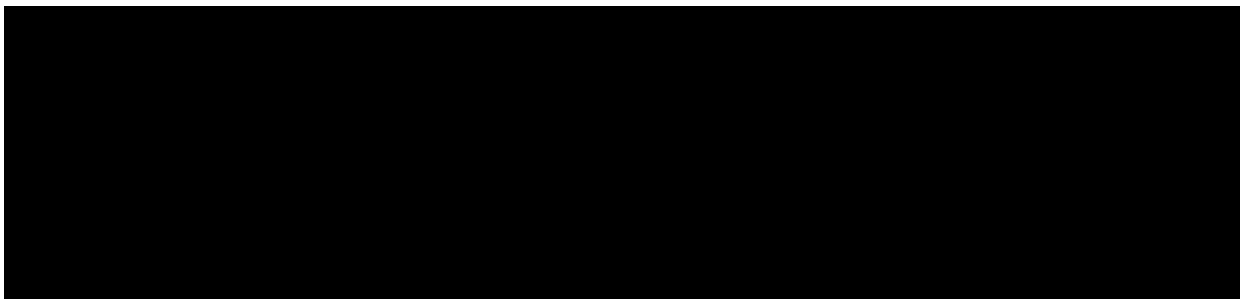
The C_{tau} concentrations observed on Day 15 through Day 36 will be compared with the average C_{tau} levels for the rest of the period to determine the time at which steady state was achieved. The following orthogonal Helmert transformation contrasts that compare each day (8, 15, 22, 29 and 36) to the mean C_{tau} concentrations over all subsequent time points will be tested for each treatment group:

- Day 8 C_{tau} value vs. the average of Day 15 through Day 36: C′1 = (1, -1/4, -1/4, -1/4, -1/4)
- Day 15 C_{tau} value vs. the average of Day 22 through Day 36: C′2 = (0, 1, -1/3, -1/3, -1/3)
- Day 22 C_{tau} value vs. the average of Day 29 through 36: C′3 = (0, 0, 1, -1/2, -1/2)
- Day 29 C_{tau} value vs. Day 36: C′4 = (0, 0, 0, 1, -1)

Testing of the contrasts will proceed in the order shown. The first non-significant comparison ($p > 0.05$) will be interpreted as the day (8, 15, 22, or 29) at which steady-state concentrations were attained.

The LS mean estimate associated with the contrasts and their corresponding 90% confidence intervals, the p-value for the difference of the least squares means (LSMs) (ln transformed scale), and the geometric mean ratios and their 90% confidence intervals will be provided for each treatment group. The LSM estimates and CI limits for the natural log values will be exponentiated. For the geometric mean ratio and its CI limits, the natural log values will be exponentiated and multiplied by 100.

Example SAS code for the steady-state assessment of Treatment A in Period 1 or Treatments B or C in a specific period:



Where

[redacted]

Example SAS code for the steady-state assessment of Treatments B or C with data from both Period 2 and Period 3:

[redacted]

Where

[redacted]

6.10.3 Statistical Assessment of Bioequivalence at Steady-State

To examine the relative bioavailability at steady state of the 5 and 10 mg/day TDS (Tests) relative to Aricept (Reference), plasma donepezil exposure as characterized by $AUC_{0\text{-}168,ss}$ and $C_{max,ss}$ 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 $AUC_{0\text{-}168,SS}$ and $C_{max,ss}$ ($C_{max,ss}$ for informational purposes). Forest plots presenting the point estimate and 90% confidence intervals for $AUC_{0\text{-}168,ss}$ and $C_{max,ss}$ will be constructed for the comparisons between the 5 mg/day and 10 mg/day donepezil TDS applications (Tests) and oral Aricept® (Reference).

6.10.4 Subgroup Analyses

Assessment of exposure across gender, ethnicity and age will be explored using the steady state PK parameters $AUC_{0\text{-}168,ss}$ and $C_{max,ss}$. Subset analyses will include treatments B and C only.

Gender Analysis
To assess exposure across gender, adding gender and gender by treatment interaction to the bioequivalence models allows for testing gender effects across and within the study treatment. In the model, gender and gender by treatment interaction effects will be estimated using least squares means and tested using a significant level of alpha = 0.05. The following SAS code details the testing approach within the standard BE models:

[redacted]

Where

[redacted]

In addition, box-plots of the parameters will be generated for each treatment by gender.

Ethnicity Analysis
Similar to gender above, effects of ethnicity (Hispanic or Latino vs. Not-Hispanic or Latino) will be explored.

Age Analysis
To examine the potential effect of age on donepezil steady-state PK for the B and C treatments, a three-step assessment procedure will be undertaken:

1. Test slopes-equal-to-zero hypothesis for each treatment: This is designed to determine if a model without the covariate of age can be used to adequately describe the PK parameters (i.e. test the slopes-equal-to-zero hypothesis for each treatment). To achieve this objective an additional fixed effect (age*treatment) will be added to the Treatment B vs. Treatment C ANOVA model described in Section 6.10.1. If the hypothesis that all

slopes are zero is accepted, a common slope model will be fit to the data and the slope-equal-to-zero hypothesis will be tested (Step 3 below).

2. If the hypothesis that all slopes are equal to zero was rejected in Step 1 (i.e. 1 or more of the slopes were not 0), the hypothesis that the slopes are equal will be tested. An ANCOVA will be performed on the natural logarithms of the PK parameters with age being added to the model used in Step 1. If the slopes are determined to be unequal, the treatment-specific slopes and intercepts from the unequal slopes model (Step 1) will be used to describe the relationship between age and the natural log transformed PK parameter for each treatment.
3. If the null hypothesis of slopes equal to zero is not rejected (Step 1) or if the test of the equal slopes hypothesis indicates insufficient evidence to reject the assumption of equal slopes (Step 2), then a common slope model will be fit to the data and the hypothesis that the common slope is 0 will be tested. ANCOVA will be performed on the natural logarithms of the PK parameters with age being added as a covariate to the Treatment B vs. Treatment ANOVA model described in Section 6.10.1. If the common slope is determined to not be 0, the intercept for each treatment and the common slope will bebe reported. If the treatment-by-age effect in Step 2 shows the slopes can be assumed to be equal (i.e., non-significant treatment-by-age interaction), then a simplified common slope model will be fitted where the age contribution can be assessed (testing the hypothesis that the age coefficient, common slope, is zero).

The following outlines the testing process.

For Step 1, the following SAS code is provided to clarify the approach for determining if any of the treatment specific slopes are not equal to zero:

[redacted]

Where

[redacted]

For a given natural log transformed PK endpoint, if the age*trt effect is significant then it can be concluded that at least one treatment specific slope is not equal to zero and Step 2 of the process is implemented. If the test is not significant then all slopes can be assumed as zero, a common slope model will be fit to the data (Step 3), and the hypothesis that the common slope is zero will be tested.

For Step 2, if the one or more of the slopes are non-zero in Step 1, the following code sets up the test to determine whether the slopes are equal:

[redacted]

Where

[redacted]

If the age*trt effect is significant, then it will be concluded that the relative effect of age on the natural log transformed PK endpoint differs by treatment (i.e., the slopes are not equal); in this case the treatment-specific slopes and intercepts from the unequal slopes model (Step 1) will be used to describe the relationship between age and the natural log transformed PK parameter for each treatment.

For Step 3, if the slopes equal to zero is not rejected (Step 1) or if the age contributions across treatments, slopes, are concluded to be equal (Step 2), then the following code fits the common slope model:

For the ANOVA (Treatment B vs. Treatment C):

[redacted]

Where

[redacted]

Scatter plots of the PK results by treatment and age, with regression lines displayed, will be provided.

For effects of gender or ethnicity on exposure the least squares geometric means (LSGM) of the PK parameters for each gender or each ethnicity group will be reported. Point estimates and 90% Confidence Intervals (CI) for the ratios of geometric means (Female vs. Male or Hispanic or Latino vs. Not-Hispanic or Latino) will be provided. The results from Type 3 Tests of Fixed Effects will also be reported with p-values to indicate if significant effects from gender, ethnicity, or age for each treatment exist.

6.11 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Population.

6.11.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has a new onset during the study between the initiation of study drug and the follow-up visit.
- Any pre-existing AE that has worsened in severity on or after the initiation of study drug till the follow-up visit.

The following rules will be used to assign a TEAE to a treatment:

- A TEAE will be assigned to the treatment received immediately before onset.
- Any TEAE reported within Period 1, Day 36, when no treatment is administered, will be attributed to the last treatment received before Day 36 began.
- If the severity of a TEAE increases in a later period the TEAE at the increased severity also will be assigned to the treatment received immediately before the increase in severity.

All TEAEs are defined as being definitely, probably, possibly related or unrelated to the study drug. If an AE has missing relationship it is assumed to be definitely related to the study drug for analysis purposes. Additionally, any SAE considered definitely, probably, or possibly related to the study drug will also be classified by the Sponsor as either "expected" or "unexpected" upon review by the medical monitor.

Adverse event severity will be graded as Grade 1: Mild, Grade 2: Moderate, or Grade 3: Severe or Medically Significant but not immediately life-threatening. Maximum severity will be assumed for an AE with missing severity.

All AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA version 23.1, updated to include activities related to COVID-19) by SOC and PT.

The following tables will be presented for AEs by treatment and overall using the Safety Population:

- Overall incidence and the number of AEs, SAEs, TEAEs leading to withdrawal.
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events and "expected or unexpected" classification
- TEAE by system organ class and preferred term by nearest relationship to study drug, incidence and number of events
- TEAE by system organ class, preferred term and maximum severity, incidence
- TEAEs leading to early withdrawal by system organ class and preferred term, incidence
- Listing of Serious TEAEs (presented in the Table section of the appendices)
- Listing of Deaths (produced only if necessary and presented in the Table section of the appendices)
- Listing of TEAEs leading to early termination by system organ class and preferred term, incidence

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

If more than one AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

All AEs will be listed.

6.11.2 Laboratory Data

Samples for clinical laboratory tests will be collected at screening, prior to start of Period 1 treatment (Treatment A), at the end of treatment within each study period, and in the event of premature study termination. Descriptive statistics for the the observed values and change from baseline (continuous data) will be presented by treatment for hematology, serum chemistry, coagulation, and urinalysis parameters at the following time points:

- Screening,
- Baseline (last available measurement prior to start of Period 1 treatment),
- End of treatment (Day 36 after TDS application/first dose within study period),
- Early termination (last available sample collected for subjects who prematurely terminated from the study).

Each measurement (continuous data) will be classed as below (low), within (normal), or above (high) normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from Screening visit to the End of Treatment (EoT) or ET visit will be presented.

A listing of any abnormal laboratory measurements recorded throughout the study will be presented.

All laboratory data, including serology, urine drug screening tests, COVID-19 testing data and pregnancy test data will be listed.

6.11.3 Vital Signs

Vital signs will be collected at screening, prior to start of Period 1 treatment (Treatment A), on the day of first TDS application/first dose within study period, and weekly thereafter (i.e., on Days 1, 8, 15, 29, and 36 within study period). Additionally, vital signs will be collected in the event of premature study termination. Vital signs include the following endpoints:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

- Pulse rate (bpm)
- Respiration rate (breath/min)
- Oral temperature (C)

Descriptive statistics will be presented for observed values and changes from baseline by treatment at the following time points for subjects in the Safety Analysis Population:

- Screening,
- Baseline (last available measurement prior to start of Period 1 treatment),
- Day of first TDS application (Treatments A and B)/first dose (Treatment C) within study period)
- Days 1, 8, 15, 22, 29, and 36 within study period
- Early Termination (last available on-treatment vital signs collected for subjects who prematurely terminate from the study)

All vital signs data will be listed.

6.11.4 Electrocardiogram Data

Twelve-lead electrocardiograms (ECGs) will be obtained at screening, prior to start of Period 1 treatment (Treatment A), and at the end of treatment (Day 109). Additionally, ECGs will be obtained in the event of premature study termination. Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated overall at the end of treatment (Study Day 109):

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTcB interval (ms) [Bazett's formula]
- QTcF interval (ms) [Fridericia's formula]

If an ECG measurement was repeated, only the repeated measurement was recorded.

Shift tables in relation to the overall interpretation (Normal, Abnormal NCS, and Abnormal CS) from baseline to end of treatment (Study Day 109) will be presented.

All ECG data, including details of any abnormalities, will be listed.

6.11.5 Physical Examination

All physical examination data will be listed, including any clinically significant findings.

6.11.6 C-SSRS

All C-SSRS data will be listed.

6.11.7 Skin Tolerability Assessments

Skin tolerability assessments will be summarized descriptively by treatment using the Skin Irritation Population for each post removal assessment time point as follows:

- The frequency distribution of Dermal Response and Other Effects scores (number, % by category) will be summarized by post removal time point (0.5, 24, 48, and 72 hours post removal)
- The frequency distribution (number, % by score category) of the combined skin irritation score will be summarized by post removal time point (0.5, 24, 48, and 72 hours post removal). The combined skin irritation score at a given time point can range from 0 to 10 and is calculated as the sum of:
    - Dermal Response score which ranges from 0 (none or no evidence of irritation) to 7 (strong reaction spreading beyond the application site
    - Other Effects scores which ranges from 0 (slightly glazed appearance) to 3 (glazing with fissures, film of dried serous exudate covering all or part of the TDS site, or small petechial erosions and/or scabs)
- Number (%) of subjects with a combined irritation score of ≥3 at 30 minutes after TDS removal
- Number (%) of subjects with one or more combined skin irritations scores of ≥3 at any time point between 30 minutes and 72 hours after TDS removal)
- Number (%) of TDS that were removed due to an unacceptable degree of skin irritation

All skin tolerability assessment data will be listed.

6.11.8 Skin Photography

All skin photography data collected in the CRF will be listed, including the assessment date/time and any recorded comments.

6.12 Adhesion Assessments

TDS observed adhesion score results (i.e., observed percent adhesion with 0% adhesion assigned to all remaining time points during the wear period in the event of complete detachment) for each TDS will be summarized by treatment as follows using the Adhesion Population:

- 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 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

In addition to the observed adhesion score, a modified adhesion score will be calculated as follows: the lowest observed 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. The modified adhesion score results for each TDS will be summarized as follows for the Adhesion Population:

- Summary statistics (mean, SD, minimum, Q1, median, Q3, maximum) for the mean adhesion score computed based on the modified adhesion scores.
- Adhesion score distribution at each adhesion measurement time point post patch application.
- Average modified adhesion score at each adhesion measurement time point post patch application.

All adhesion assessment data (observed adhesion scores as well as the modified adhesion scores as described previously) will be listed.

Within each treatment, 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 (CI) 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 exceeds 80%, then it will be concluded that at least 80% of patches are at least 75% adhered throughout the wear period.

The 95% lower confidence limit will be determined using the Jeffreys prior method. The Jeffreys interval has a Bayesian derivation, and has good frequentist properties (Brown, Cai, Dasgupta 2001; Cai 2005). It is obtained using the non-informative Jeffreys prior for the binomial proportion p, namely a Beta distribution with parameters (½, ½). It is a conjugate prior with a posterior distribution for p that is Beta (X+½, n-X+½), where n is the number of TDS in the Adhesion Population for the treatment and X is the number of TDS with at least 75% adhesion throughout the wear period. The 95% lower confidence limit (CL) will be formed as follows:

$$CL = Beta(0.05; X + ½, n – X + ½)$$

where in the event that x=0, the lower limit is defined to be 0.

The Jeffreys one-sided CI has been recommended by Cai (2005). It is one of the few CI methods with the advantage of being equal-tailed (i.e., the probabilities of the interval lying above or below the true value are equal). The Wilson score interval, for example, has good coverage probabilities as a method for constructing two-sided confidence intervals for p, but has a systematic bias in that it is centered too close to p=0.5 making it unsuitable for construction of a one-sided interval. Similarly, the one-sided Wald interval and the likelihood ratio interval (formed by inversion of the likelihood ratio test) also have pronounced systematic bias (Cai 2005; Newcombe 1998).

Adhesion results from 3 previous studies are available (Table 1). In Study P-15086 (Periods 2 and 3 where the incidence of patch taping and smoothing was extremely low), point estimates of the probability that a randomly selected TDS remains at least 75% adhered during the 7-day wear period were 0.94 (32/34) for the 5 mg/day TDS and .96 (126/135) for the 10 mg/day TDS. In study P-16010, estimates that patches were at least 80% adhered throughout the 7-day wear period were 0.94 (80/85) and 0.91 (307/338) for the 5 mg/day and 10 mg/day TDS, respectively. The estimate (at least 80% adhered throughout the wear period) for the 10 mg/day TDS applied to the back in Study P=15086 was 0.85 (51/60).

Subjects received 5 mg/day TDS during Week 1 and a 10 mg/day TDS weekly during Weeks 2-5 in studies P-15086 and P-16010. Adhesion results show some indication of clustering within subject in Study P-16010 but not in Study P-15086. Individual subjects that had adhesion <75% (<80% in Study P-16010) during the TDS wear period are listed by week in Table 2. In Study P-15086, 5 TDS (10 mg/day) from 5 different subjects had 10 mg/day patches that were <75%

adhered at some point during the wear period. In contrast, there were 31 TDS (10 mg/day) from 19 subjects that were <80% adhered during the wear period in Study P-16010.

Table 1. Adhesion Results from Studies P-15086, P-16010, and P-16012

TDS Application Week	P-15086 (Periods 2 and 3) [1] Adhered >75%	$\hat{p}_{0.75}$	Study P-16010 [2] Adhered >80%	$\hat{p}_{0.80}$	Study P-16012 [2] Adhered >80%	$\hat{p}_{0.80}$
Week 1	32/34	0.94	80/85	0.94	51/60	0.85
Week 2	33/34	0.97	76/85	0.89		
Week 3	31/33	0.94	75/85	0.88		
Week 4	31/32	0.97	78/85	0.92		
Week 5	31/32	0.97	78/83	0.94		
Weeks 2-5	126/131	0.96	307/338	0.91		

[1] In Study P-15086, whole-patch adhesion was measured every 12 hours on a 5-point scale (0=100% adhered; 5=0% adhered). A score <2 at all assessment time points indicated that a patch was >75% adhered throughout the wear period. Subjects had 5 mg/day patches (50 cm^2 active drug area) applied during Week 1 and 10 mg/day patches (105 cm^2active drug area) applied weekly during Weeks 2-5.
[2] In Studies P-16010 and P-16012, whole-patch adhesion was measured every 12 hours on an 11-point scale (0=100% adhered; 11=0% adhered). A score <3 at all assessment time points indicated that a patch was >80% adhered throughout the wear period. In study P-16010, subjects had 5 mg/day patches (53.5 cm^2 active drug area) applied during Week 1 and 10 mg/day patches (107 cm^2active drug area) applied weekly during Weeks 2-5. In Study P-16012, patches applied to the back (10 mg/day patches; 107 cm^2 active drug area) during a one-week treatment period are included.
Source: Table 14.3.9.3.1 (Study P-15086); Table 14.3.9.1.1 (Study P-16010); Table 14.3.9.1.1 (Study P-16012)

Study CL-P-20004 will enroll approximately 60 subjects, with around 48 subjects expected to complete the 109-day in-clinic study. Prior single-dose crossover studies conducted by the Sponsor indicate that most dropouts occur during the first one to two treatment periods. As a result, approximately 55 subjects are expected to have TDS included in the Adhesion Population for TDS A (5 mg/day TDS), and approximately 50 subjects are expected to have TDS included in the Adhesion Population for TDS B (10 mg/day TDS). The number of 5 mg/day TDS (TDS A) in the Adhesion Population will be approximately 270, and the number of 10 mg/day TDS (TDS B) in the Adhesion Population will be approximately 245.

Based on the three previous studies (Table 1), the point estimate for p is expected to be 0.90 – 0.95 (i.e., fewer than 13 and 11 TDS are expected to have < 75% adherence at one or more adhesion assessment time points during the wear period for TDS A and TDS B, respectively).

In the range for p that is expected in the current study, the Jeffreys lower confidence limit should provide good coverage probability (Cai 2005; Newcombe 2011).

As a sensitivity analysis, the Clopper Pearson method of constructing the 95% lower confidence limit also will be implemented for each treatment. The Jeffreys prior confidence interval can be regarded as a continuity-corrected version of the Clopper–Pearson confidence interval and is always contained within the Clopper-Pearson confidence interval (Brown et al. 2001). This one-sided 95% Clopper-Pearson CI method is very conservative and has coverage probability ≥95% for all p between 0.0 and 1.0.

As a second sensitivity analysis, a one-sided 95% confidence interval that takes into account clustering of adhesion failures (i.e., TDS with <75% adhered during the wear period) within subject will be presented.

A generalized linear mixed model (GLMM) analysis of the probability that a patch is at least 75% adhered during the entire wear period will be used. The GLMM will model variation at both the individual and patch level. The GLMM will assume that each subject has an underlying, unobservable probability that governs the tendency for a patch to remain at least 75% adhered during the wear period. This probability is assumed to vary from subject to subject.

Let π_i denote the probability that a patch applied to the i^{th} subject will remain at least 75% adhered during the wear period. Let y_{ij} be the response variable for the j^{th} patch applied to the i^{th} subject:

$$y_{ij} = \begin{cases} 1 \text{ if the TDS is at least 75\% adhered throughout the wear period} \\ 0 \text{ if the TDS is less than 75\% at some point during the wear period} \end{cases}$$

The number of patches applied to the i^{th} subject with "favorable" adhesion (i.e., $y_{ij} = 1$), has a binomial distribution conditional on the random effect of subject:

$$y_i \mid s_i \sim \text{Binomial}(n_i, \pi_i)$$

where n_i is the number of patches applied to the i^{th} subject. In the current study, n_i is usually 5 but can range from 1 to 5).

Since the log likelihood function of a binomial random variable with n Bernoulli trials and favorable outcome probability π is linear in the logit, $\log(\pi/(1-\pi))$, a linear model will be fit to the logit.

Using the logit link function, a conditional GLMM for the adhesion analysis is as follows:

$$\eta_i = \log\left[\frac{\pi_i}{(1-\pi_i)}\right] = \eta + s_i$$

where η is the intercept and s_i is the effect of the i^{th} subject assumed to be independent, identically distributed $N(0,\sigma_s^2)$.

Here s_i is a latent variable centered at 0 that quantifies an individual subject's tendency (i.e., probability) for having an applied TDS remain at least 75% adhered during the 7-day wear period in relationship to other subjects. Variation in s_i, σ_s^2, represents variation in this propensity among subjects.

The inverse link function for this logistic model will be used to estimate π (Stroup et al 2018). From the link function, we have:

$$\hat{\pi} = {}^{1}/_{(1 + e^{-\hat{\eta}})}$$

with standard error estimate

$$\text{SE}[\hat{\pi}] = [\hat{\pi}(1 - \hat{\pi}) * SE(\hat{\eta})$$

and a 90% two-sided confidence interval obtained by applying the inverse of the link function to the upper and lower confidence bounds of the logistic-scale 90% two-sided confidence interval.

[redacted]

[redacted]

6.13 Duration of Patch Wear and Patch Detachment

Duration of patch wear will be summarized by treatment for the Adhesion Population. Total duration will be calculated as follows:

$$Total\ Duration\ = (removal\ date/time) - (application\ date/time)$$

Total duration will be reported in days to two decimal places.

All TDS detachment data will be listed including:

- Descriptions of circumstances related to detachment, including full detachment
- Date and time of application
- Date and time of removal/full detachment

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

No changes to the planned protocol analysis have been identified.

8 REFERENCES

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6. Newcombe RG Measures of location for confidence intervals for proportion. Communications in Stat – Theory and Methods. 2011;40:1743-1767.
7. Stroup WW, Milliken GA, Classen EA, Wolfinger RD. SAS for Mixed Models: Introduction and Basic Applications. Cary, NC: SAS Institute Inc. 2018.

9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

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Items in bold are not table titles but references to the section headings within eCTD.			
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	Not Applicable		
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Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
	Following TDS Application) and after QD Administration of 10 mg Aricept on Weeks 1 through 5 (Days 1-36 Following First Dose) for Individual Subjects on Linear Scale - PK Population		
14.4.28	Plasma Donepezil Concentration-Time Data in Plasma after 5 mg/day (Dose-Normalized)[1] and 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) and after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) for Individual Subjects on Linear Scale - PK Population	IP	
14.4.29	Plasma 6-O-Desmethyl Donepezil Concentration-Time Data in Plasma (Week 5) after 5 mg/day (Dose-Normalized)[1] and 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) and after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) for Individual Subjects on Linear Scale - PK Population	IP	
14.4.30	Forest Plot of Donepezil Exposure Comparing 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) and after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) – Relative Bioavailability Population	IP	
14.4.31	Forest Plot of Donepezil Exposure Comparing 5 mg/day TDS Application (Dose-Normalized[1]) on Week 5 (Days 29-36 Following TDS Application) and after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) – Relative Bioavailability Population	IP	
14.4.32	Forest Plot of 6-O-Desmethyl Donepezil Exposure Comparing 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) and after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) – Relative Bioavailability Population	IP	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.33	Forest Plot of 6-O-Desmethyl Donepezil Exposure Comparing 5 mg/day TDS Application (Dose-Normalized[1]) on Week 5 (Days 29-36 Following TDS Application) and after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) – Relative Bioavailability Population	IP	
14.4.34	Subgroup Analysis: Box-Plot of Donepezil Cmax,ss and $AUC_{0\text{-}168,ss}$ at Steady State (Week 5) by Gender and Treatment – Relative Bioavailability Population	IP	
14.4.35	Subgroup Analysis: Box-Plot of Donepezil Cmax,ss and $AUC_{0\text{-}168,ss}$ at Steady State (Week 5) by Ethnicity and Treatment – Relative Bioavailability Population	IP	
14.4.36	Subgroup Analysis: Estimated Regression Lines with Least Squares Means for $C_{max,ss}$ at Steady State (Week 5) versus Age by Treatment- Relative Bioavailability Population	IP	
14.4.37	Subgroup Analysis: Estimated Regression Lines with Least Squares Means for $AUC_{0\text{-}168,ss}$ at Steady State (Week 5) versus Age by Treatment- Relative Bioavailability Population	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition – Randomized Population	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Randomized Population	IP	
16.2.2.2	Informed Consent and Eligibility Criteria - Randomized Population		
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Populations	IP	
16.2.4	**Demographic Data**		
16.2.4.1	Demographics – Randomized Population	IP	
16.2.4.2	Baseline Characteristics – Randomized Population	IP	
16.2.4.3	Medical History – Safety Analysis Population	IP	
16.2.4.4	Pregnancy – Safety Analysis Population	IP	
16.2.4.5	Non-Pharmacological Procedures – Safety Analysis Population	IP	
16.2.4.6	COVID-19 – Safety Analysis Population	IP	
16.2.5	**Compliance and/or Drug Concentration Data**		
16.2.5.1	TDS Application/Removal and Treatment C (oral Aricept tablets)– Safety Analysis Population	IP	
16.2.5.2	PK Sampling Times – Safety Analysis Population	IP	
16.2.5.3	Prior and Concomitant Medications – Safety Analysis Population	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Plasma Donepezil Concentration-Time Data Listing by Subject – PK Population	IP	
16.2.6.2	Dose-Normalized Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data Listing by Subject after 5 mg/day TDS Application– PK Population	IP	
16.2.6.2	Plasma Terminal Elimination Rate of Donepezil for Individual Subjects – PK Population	IP	
16.2.6.3	PK Output Text – PK Population	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.4	SAS Output for Treatment Comparisons – Relative Bioavailability Population	IP	
16.2.6.5	SAS Output Text for Relative Bioavailability Assessment– Relative Bioavailability Population	IP	
16.2.6.6	SAS Output Text for Steady-State Assessment– PK Population	IP	
16.2.6.7	SAS Output Text for Subgroup Analysis: Gender Comparison – PK Population	IP	
16.2.6.8	SAS Output Text for Subgroup Analysis: Ethnicity Group Comparison – PK Population	IP	
16.2.6.9	SAS Output Text for Subgroup Analysis: Age Comparison – PK Population	IP	
16.2.6.10	Subjects Excluded from the Pharmacokinetic and Relative Bioavailability Populations	IP	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Events – Safety Analysis Population	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology – Safety Analysis Population	IP	
16.2.8.2	Serum Chemistry – Safety Analysis Population	IP	
16.2.8.3	Coagulation – Safety Analysis Population	IP	
16.2.8.4	Abnormal Clinical Laboratory Values	IP	
16.2.8.5	Urinalysis – Safety Analysis Population	IP	
16.2.8.6	Drug and Alcohol Screen – Safety Analysis Population	IP	
16.2.8.7	Serology – Safety Analysis Population	IP	
16.2.8.8	Vital Signs – Safety Analysis Population	IP	
16.2.8.9	12-Lead ECG - – Safety Analysis Population	IP	
16.2.8.10	Physical Examination – Safety Analysis Population	IP	
16.2.8.11	C-SSRS (Part 1, 2, or 3 of 3)– Safety Analysis Population	IP	
16.2.8.12	Skin Photography – Safety Analysis Population	IP	
16.2.9	**Adhesion and Skin Assessment**		
16.2.9.1	Skin Irritation Assessments – Skin Irritation Population	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.9.2	Adhesion Assessments – Adhesion Population	IP	

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WORLDWIDE CLINICAL TRIALS	Sponsor:	Corium, Inc.
	Protocol Number:	CL-P-20003
POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM		

Statistical Analysis Plan
Post Database Lock Addendum

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

Protocol Number: CL-P-20003

Final Version, dated 28-SEP-2020

Amendment #1 dated: 26-OCT2020

Protocol Clarification Memo #1, dated 30-OCT-2020

SAP Version: 1.0, Issue Date: 9-MAR-2021

Addendum Number: 1

Addendum Version: 1.0

Addendum Issue Date: 15-JUL-2021

Previous Addenda

NA

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Corium, Inc.
	Protocol Number:	CL-P-20003
POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM		

1. BACKGROUND

This document details changes and / or additions to the planned statistical analyses for Corium, Inc. protocol CL-P-20003, a study titled "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" previously described in V1.0 of the Statistical Analysis Plan (SAP) dated 9-MAR-2021.

1.1 Rationale for Addendum:

i. Changes made to the SAP in Sections: 6.2.11.1, 6.10.1, 6.10.3, 6.11.1, and 6.12
ii. To update the changes in title and numbering of three tables
iii. To update the changes made to table, figure and listing shells

2. CHANGES TO EXISTING SAP

2.1 Change 1 in Section 6.2.11.1

2.1.1 Original text

Percent peak-to-trough fluctuation within the 168 h wear period at steady-state on Week 5, calculated as:

$FLUCP_{,ss} = (C_{max,ss}/C_{min,ss})/C_{avg}$ x 100, where $C_{min,ss}$ and $C_{max,ss}$ are obtained between 0 and tau (168 h)

Percent peak-to-trough fluctuation on Day 35, calculated as:

$FLUCP_{,ss} = (C_{max,ss}/C_{min,ss})/C_{avg}$ x 100, where $C_{min,ss}$ and $C_{max,ss}$ are obtained between 0 and tau (24 h)

2.1.2 New text

Percent peak-to-trough fluctuation within the 168 h wear period at steady-state on Week 5, calculated as:

$FLUCP_{,ss} = (C_{max,ss}-C_{min,ss})/C_{avg}$ x 100, where $C_{min,ss}$ and $C_{max,ss}$ are obtained between 0 and tau (168 h)

Percent peak-to-trough fluctuation on Day 35, calculated as:

$FLUCP,ss = (C_{max},ss-C_{min},ss)/C_{avg}$ x 100, where $C_{min,ss}$ and $C_{max,ss}$ are obtained between 0 and tau (24 h)

2.2 Change 2 in Section 6.10.1

2.2.1 Original text

Intraclass Correlation = ($Var_{Subject(sequence)}$ - $Var_{Subject(sequence)}$) / ($Var_{Subject(sequence)}$ + $Var_{Subject(sequence)}$.)

2.2.2 New text

Intraclass Correlation = ($Var_{Subject(sequence)}$ - $Var_{Residual}$) / ($Var_{Subject(sequence)}$ + $Var_{Residual}$)

2.3 Change 3 in Section 6.10.3

2.3.1 Original text

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 Cmax,ss, it is stipulated that mean steady-state donepezil Cmax,ss after patch administration should remain between the steady-state $C_{max,ss}$ and $C_{min,ss}$ after daily oral Aricept® administration.

2.3.2 New text

Original text removed.

2.4 Change 4 in Section 6.11.1

2.4.1 Original text

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has a new onset during the study between the initiation of study drug and 5 days after the last dose of study drug.
- Any pre-existing AE that has worsened in severity on or after the initiation of study drug within 5 days after the last dose of study drug.

2.4.2 New text

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has a new onset during the study between the initiation of study drug and the follow-up visit.
- Any pre-existing AE that has worsened in severity on or after the initiation of study drug till the follow-up visit

2.5 Change 5 in Section 6.12

2.5.1 Original text

proc glimmix data=adh_count method=quad;

class subjid;

model yi/ni (event='1') = / ;

random intercept / subject=subjid

estimate 'pop average proportion' intercept 1 / cl ilink alpha=0.10;

run;

2.5.2 New text

In proc glimmix data=adh_count;

class subjid;

model yi/ni = / ;

random intercept / subject=subjid

estimate 'pop average proportion' intercept 1 / cl ilink alpha=0.10;

run;

3. ADDITIONS TO EXISTING SAP

No additions to existing SAP.

4. CHANGES TO TABLES, FIGURES AND LISTINGS (TFL) SHELL TABLE OF CONTENT (TOC) WITHIN SAP

Table/Figure/Listing Shells	Changes Made
Table 14.1.1.1	Changes on format and contents of Parameter labels and addition of footnote 2
Table 14.1.1.2	Removed
Table 14.1.1.3	Changes: Table Number from 14.1.3 to 14.1.1.2; Table title modified, Treatments column deleted, one footnote added
Table 14.1.2.1	Change "Randomized Population" to "Safety Analysis Population" in the table title, and added a footnote for percent calculations

Table 14.1.3.1	Added a footnote: Percentage for Fertility Status is calculated from the number of females
Table 14. 3.2.1	Added footnotes: "Subjects are counted once within a system organ class and once for each unique preferred term. Percentages are based on the number of subjects in the Safety Analysis Population by treatment and overall."
Table 14.3.5.1	Footnotes modified
Table 14.3.6.1	Table title and Visit label modifications
Table 14.3.7.12	Added footnote: "Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B."
Table 14.3.7.13	Added footnote: "Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B."
Table 14.3.7.14	Added footnote: "Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B."
Table 14.3.7.20	Renumber Table 14.6.1 to Table 14.3.7.20
Table 14.3.7.21	Renumber Table 14.6.2 to Table 14.3.7.21
Table 14.6.1	Removed
Table 14.6.2	Removed
Figure 14.4.3	Planned Figure: Mean Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data after 5 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) on Linear Scale - PK Population Updated Figure: Mean Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after 5 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) on Linear Scale - PK Population
Figure 14.4.4	Planned Figure:

	Mean Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data after 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) on Linear Scale - PK Population Updated Figure: Mean Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) on Linear Scale - PK Population
Figure 14.4.5	Planned Figure: Mean Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) on Linear Scale - PK Population Updated Figure: Mean Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) on Linear Scale - PK Population
Figure 14.4.22	Planned Figure: Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data after 5 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) for Individual Subjects on Linear Scale -PK Population Updated Figure: Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after 5 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) for Individual Subjects on Linear Scale - PK Population
Figure 14.4.23	Planned Figure: Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data after 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) for Individual Subjects on Linear Scale - PK Population Updated Figure: Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after 10 mg/day TDS Application on Week 5 (Days 29-36 Following TDS Application) for Individual Subjects on Linear Scale - PK Population

Figure 14.4.24	Planned Figure: Plasma Donepezil and 6-O-Desmethyl Donepezil Concentration-Time Data after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) for Individual Subjects on Linear Scale - PK Population Updated Figure: Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after QD Administration of 10 mg Aricept for Week 5 (Days 35-36 Following First Dose) for Individual Subjects on Linear Scale - PK Population
Listing 16.2.1.1	Three columns were removed: "Safety Analysis Population", "Pharmacokinetic (PK) Population", and "Relative Bioavailability (BA) Population" .
Listing 16.2.2.1	Added one column (PD Code) added Study Day to PD Date with a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.3.1	Both PK Population and BA population were split into two columns (Primary and Secondary)
Listing 16.2.4.4	Added two columns: "Period | Treatment" and "Assessment Date/Time (Study Day)"
Listing 16.2.4.6	Added two footnotes: 1) # Study day relative to each treatment period start date; 2) Note: Visits marked as "Extension Days" indicate a 7-8 day gap between the end of Period 2 (Day 36 relative to start of Period 2) and the start of Period 3
Listing 16.2.5.1	Listing title changed to: "TDS Application/Removal and Treatment C (Oral Aricept Tablets); One footnote added ":# Study day relative to each treatment period start date"; Treatment C was included in the listing.
Listing 16.2.5.2	Changed the Column header "Study Day" to "Visit" and added Study Day to "Sample Date/Time" column header [Sample Date/Time (Study Day)]
Listing 16.2.5.3	Added footnote: "# Study day relative to each treatment period start date"
Listing 16.2.6.10	Added Listing: Subjects Excluded from the Pharmacokinetic and Relative Bioavailability Populations
Listing 16.2.7.1	Added footnote: "# Study day relative to each treatment period start date"

Listing 16.2.8.1	Added "Period | Treatment" column and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.2	Added "Period | Treatment" column, removed "CS?" column, and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.3	Added "Period | Treatment" column, removed "CS?" column, and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.4	Added "Period | Treatment" column, removed "CS?" column, and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.5	Added "Period | Treatment" column, removed "CS?" column, and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.6	Added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.9	Added "Period | Treatment" column, removed the Overall Interpretation" Columns, and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.10	Added "Period | Treatment" column and added a footnote: "# Study day relative to each treatment period start date"
Listing 16.2.8.11	Added "Period | Treatment" to Visit column, added a "Reference" column, added two footnotes: "# Study day relative to each treatment period start date" and "[1]Reference - Reference timeframe: 6 Months = Past 6 months; Last Visit = Since last visit"
Listing 16.2.8.12	Added column "Layers of TDS Attached to Each Other?" and added a footnote: "# Study day relative to each treatment period start date"
Listing 12.2.9.1	Replace "Hours Post TDS Removal" with "Study Day" in the "Date/Time Assessment" column; removed the two "What was present?" columns; added a footnote: "# Study day relative to each treatment period start date"

5. CHANGES TO SAP TFL SHELL VERSIONS

Previous version of TFL Shells:	New version of TFL shells:
CL-P-20003_SAP_v1.0 [Issue date 9-MR-2021]	CL-P-20003_SAP_v2.0 [Issue date 15-JUL-2021]

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CL-P-20003_TableShells_v1.0 [Issue date 9-MAR-2021]	CL-P-20003_TableShells_v2.0 [Issue date 15-JUL-2021]
CL-P-20003_ListingShells_v1.0 [Issue date 9-MAR-2021]	CL-P-20003_ListingShells _v2.0 [Issue date 15-JUL-2021]

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POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM

Approval for implementation of

Statistical Analysis Plan Post Database Lock Addendum

The above SAP Post Database Lock Addendum has been reviewed and approved by Worldwide:

Name of Author: [redacted]

[redacted] [redacted]

Signature: DocuSigned by: [redacted]
[redacted]
Signing Reason: I am the author of this document
Signing Time: 15-Jul-2021 | 06:34:14 PDT
28DA65A16F2043F3869417BAE8218929

Date:

Name of Author: [redacted]

Position: [redacted]

Signature: DocuSigned by: [redacted]
[redacted]
Signing Reason: I am the author of this document
Signing Time: 15-Jul-2021 | 07:36:32 PDT
A2103069EADE42BA87CC9685DDF4E5A1

Date:

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POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM

Name of Reviewer:	[redacted]
Position:	[redacted]
Signature:	DocuSigned by: [redacted] Signing Reason: I approve this document Signing Time: 15-Jul-2021 | 06:50:19 PDT 73AFDF654F3A4785974EFAECAE63CAA8
Date:	

The above SAP Post Database Lock Addendum has been reviewed and approved by the Sponsor:

Name of Sponsor:	[redacted]
Position:	[redacted]
Signature:	DocuSigned by: [redacted] Signing Reason: I approve this document Signing Time: 15-Jul-2021 | 09:47:52 EDT 80165E0DB6494EA1840E4726B67DE0F2
Date:	