CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212304Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 212304
Link to EDR	\\CDSESUB1\evsprod\nda212304 SN:0028
Submission Date	09/13/21
Submission Type	Resubmission NDA – 505(b)(2)
Brand Name	ADLARITY
Generic Name	Donepezil
Dosage Form and Strength	Transdermal Delivery System,10 mg/day and 5 mg/day
Route of Administration	Transdermal
Proposed Indication	Symptomatic treatment of mild, moderate and severe Alzheimer's Disease (AD)
Applicant	Corium Inc.
Associated IND	IND 129778
OCP Review Team	Min Li, Vishnu Sharma, Atul Bhattaram, and Bilal AbuAsal

Table of Contents

1. Executive Summary

Corium International Inc. submitted the original NDA 212304 via 505(b)(2) pathway on Sep 30, 2019 for ADLARITY®, donepezil transdermal delivery system (TDS), using ARICEPT® oral tablets as the listed drug (LD). The FDA issued a Complete Response Letter (CRL) on Jul 23, 2020, mainly because of the major difference in the manufacturing process for the tested TDS in the pivotal bioequivalence (BE) study (P-15086) from the intended commercial process for to-be-marketed product as well as other major product quality concerns.

In this resubmission, the Applicant is seeking the approval for a modified TDS product which incorporates (b) (4). The submission included: a new pivotal relative bioavailability (BA) study (Study CL-P-20003) to evaluate the steady-state pharmacokinetics (PK) of the ADLARITY TDS products (both 5 mg/day and 10 mg/day strengths once weekly) compared to Aricept tablets (10 mg once daily); two relative BA studies (Studies CL-P-20004 and CL-P-19005) to support TDS product shelf life and crystal content specifications, respectively; and a reanalysis of PK samples of a previous study (P-16010) for supportive information. This clinical pharmacology review is focused on the evaluation of the adequacy of the pivotal relative bioavailability study as well as the adequacy of the proposed switching instruction to ADLARITY TDS from ARICEPT tablet. Other clinical pharmacology components were previously reviewed by Dr. Hristina Dimova and documented in DARRTS[1].

Based on the results from Study CL-P-20003, the geometric mean ratios for the exposure metrics (i.e., C_{max} and AUC_{tau}) for donepezil at steady state met the standard bioequivalence criteria for both TDS 10 mg/day and 5 mg/day when compared to ARICEPT tablets. In addition, the C_{trough} for ADLARITY was noninferior to that for the reference product ARICEPT. The two dose strengths of ADLARITY TDS, 5 mg/day and10 mg/day, were proportional based on BE analysis after dose normalization. Although the shapes of the donepezil PK profiles of TDS and oral tablets are different, the shape difference was not considered clinically significant considering donepezil's long elimination half-life and the mechanism of action of donepezil. The active metabolite level (6-O-Desmethyl-Donepezil) observed in this pivotal study was very low (<0.3%) relative to donepezil exposure across the treatments. As a result, any potential differences in the exposure of metabolites between the oral tablets and the TDS is considered clinically insignificant. Hence, the bioequivalence assessment based on the metabolite's PK was not performed across treatments. Overall, this pivotal study (CL-P-20003) provides an adequate scientific bridge to rely on the labeling information (including safety) and efficacy of the LD product.

[1] Clinical pharmacology review in DARRTS Dated 5/28/2020

For switching from ARICEPT to ADLARITY, the proposed label instructs patients or caregivers to apply the first TDS [redacted] (b) (4) for switching to ADLARITY from donepezil tablets or donepezil orally disintegrating tablets (ODT). Based on the PK simulations conducted by the review team at different scenarios, application of the TDS patch at the same time as the last oral dose is administered could effectively offset the donepezil concentration drop below the minimum concentrations of oral treatment at steady state ($C_{trough,ss}$) at the first 10 days of the switch. Therefore, the review team recommended that the first TDS patch should be applied when administering the last oral dose.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study CL-P-20003. The OSIS noted that inspection was not warranted because the site was recently inspected (DARRTS dated 11/26/2021 and 2/18/2022)[2].

2. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA (#212304) and recommended approval based an adequate PK bridge demonstrated between the Donepezil transdermal system and the listed drug, ARICEPT tablets, for the treatment of dementia of the Alzheimer's type in patients with mild, moderate, and severe Alzheimer's Disease (AD). No post-market commitment or post-market requirement is needed.

3. Background and Regulatory History

ADLARITY Donepezil TDS is a transdermal patch product administered once a week, indicated for the symptomatic treatment of dementia of the Alzheimer's type. This is a 505(b)(2) application with reliance on the FDA's previous finding of the safety and effectiveness of ARICEPT® (NDA 020690) as the LD. Two strengths of the Donepezil TDS are proposed for marketing: 52.5 cm^2 (intended to deliver 5 mg/day); and 105 cm^2 (intended to deliver 10 mg/day).

The original NDA was submitted on Sept 30, 2019 with a pivotal relative bioavailability (BA) study (Study P-15086) to establish bioequivalence (BE) of Donepezil TDS with ARICEPT® donepezil tablets along with several clinical pharmacology studies as listed in Table 1. Based on the clinical pharmacology review for the original NDA conducted by Dr. Hristina Dimova[1], the pivotal clinical study established BE between once-weekly donepezil TDS and ARICEPT® at steady state.

[2] Consult review Bioequivalence Establishment Inspection Report Review in DARRTS dated 11/26/2021 and 2/18/2022

The original NDA received a complete response letter (CRL) on 7/23/2020[3], mainly because the TDS patches used in this pivotal study was manufactured with a different process from the proposed manufacturing process for the commercial TDS product. In the CRL, the FDA recommended conducting a new BE study with the LD, utilizing the proposed commercial product/manufacturing process. In addition, major quality issues on the TDS product including the transdermal patch design and stability were identified.

The applicant had a Type A end of review meeting with the FDA on Oct 13, 2020 and discussed the proposed plan to address the major deficiencies in the CRL. Specifically for addressing the major quality concerns, the applicant proposed (b) (4) . The applicant proposed a new pivotal relative BA study (CL-P-20003) for the modified to-be-marketed TDS product and the general approach to demonstrate bioequivalence at steady state was agreed by the Agency. Since the proposed TDS is administered by a different route from the LD, the Agency recommended measuring plasma concentrations of the active metabolite 6-Odesmethyl donepezil in the proposed pivotal PK bridging study. In addition, the applicant also proposed another relative BA study (# CL-P-20004) to support the shelf life of the (b) (4) commercial donepezil transdermal system and the general study design was considered acceptable by the FDA. The details of the meeting discussion were documented in DARRTS dated 11/10/2020.[4]

The complete response to the CRL (Class 2 resubmission, SN0028) was received from the applicant on Sept 23, 2021. To support the modified to-be-market TDS product, the applicant conducted three new relative BA studies (Studies # CL-P-20003, CL-P-20004 and CL-P-19005) and analyzed stored plasma samples that were collected during Study P-16010 (see Table 2).

Table 1 Clinical studies included in the original NDA

Study #	Study Title	Brief Description
P-15007	A Phase 1, Crossover Study to Evaluate the PK, PD and Safety of Two Formulations of a 7-Day Application of Donepezil Transdermal Delivery System Compared to Oral Administration of Aricept in Healthy Volunteers	To Assess initial TDS formulation performance Single dose
P-15081	A Phase 1 Parallel Study to Evaluate the PK, PD and Safety of Formulations of a 7-Day Application Donepezil Transdermal Delivery System (TDS) in Healthy Female	Formulation Selection Single dose

[3] Complete Response Letter documented in DARRTS dated 7/23/2020

[4] Meeting minutes Documented in DARRTS dated 11/10/2020

P-16007	A Phase 1 Study to Evaluate the Adhesion, Pharmacokinetics (PK) and Safety of a Seven-Day Application of Donepezil Transdermal Delivery System (TDS) in Healthy Volunteers	To assess adhesion, PK and safety Single dose
P-15086	A Phase 1, Randomized, Open Label, 3-Way Crossover, Pilot, Pharmacokinetic Study to Evaluate the Steady State Pharmacokinetics of a Once-Weekly Application of Corplex™ Donepezil Transdermal Delivery System Compared to Daily Oral Administration of Aricept® in Healthy Adult Subjects	Pivotal BE study for the original NDA To assess BE at Steady state BE
P-16011	A Randomized Double-Blind Study to Assess the Skin Irritation and Sensitization Potential of Once-Weekly Corplex™ Donepezil Transdermal Delivery System	To assess skin irritation/ sensitization
P-16012	A Phase 1, Crossover Study to Evaluate the Pharmacokinetics of Corplex™ Donepezil 10 mg Transdermal Delivery System Applied to Different Body Locations	Relative bioavailability study to assess the effect of application site (back, thigh, buttock) on the PK
P-16039	A Phase 1, 2-Way Crossover Study to Evaluate the Effect of Heat Application on the Pharmacokinetics of Corplex™ Donepezil 5 mg Transdermal Delivery System (TDS) in Healthy Volunteers	Relative bioavailability study to assess the effect of heat application on the PK of TDS
P-16010	A Study to Assess the Steady State Bioequivalence of Once-Weekly Corplex™ Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®	To assess safety/tolerability and adhesion The PK samples were
P-15086 Sub-Study[a]	A Phase 1, Randomized, Open Label, 2-Way Crossover Study, to Compare the Relative Bioavailability of Two Corplex Donepezil Transdermal Delivery Systems' Manufactured Using Active Pharmaceutical Ingredient from 2 Different Suppliers	Relative bioavailability to assess the PK for different API supplier - API Supplier

APPEARS THIS WAY ON ORIGINAL

Note: Corplex™ was the previous brand name proposed in the original NDA

a. The P-15086 Sub-Study was conducted as an amendment to Protocol No. P-15086.

Reference: \\CDSESUB1\evsprod\nda212304\0028\m2\25-clin-over\25-clinical-overview.pdf Page18 Table 5.

Table 2: Clinical pharmacology Studies submitted in the resubmission

Study #	Study Title	Brief Description
CL-P-20003	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	Pivotal relative bioavailability study to assess BE between the to-be-marketed TDS ((b) (4) both 5 mg/day and 10 mg/day) and ARICEPT 10 mg oral daily at steady state Multiple-dose, crossover study
CL-P-20004	A Phase 1, Open-Label, Randomized, 2-Period, Crossover Pharmacokinetic Study Comparing Two Corplex Donepezil Transdermal Delivery Systems of Different Age in Healthy Volunteers	Relative bioavailability study to compare the (b) (4) treated donepezil TDS 5 mg/day stored for about 24 months at 2-8°C to the to-be-marketed (b) (4) TDS 5 mg/day stored for about 24 months at 2-8°C Single-dose, crossover study
P-16010 [b]	A Study to Assess the Steady State Bioequivalence of Once-Weekly Corplex™ Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®	Relative bioavailability study to compare the (b) (4) TDS patches (previous to-be-market product without (b) (4)) product 10 mg/day with daily oral ARICEPT administration at steady state Multiple-dose, crossover study
CL-P-19005	A Phase 1, Randomized, Blinded, 2-Way Crossover Study to Assess the Relative Bioavailability of Corplex™ Donepezil Transdermal Delivery Systems With and Without Crystals	Relative bioavailability study to assess the PK of the TDS products 10 mg/day between the patches without crystal and with crystals represented patches (previous to-be-marketed TDS) Single-dose, crossover study

b. The safety/tolerability and adhesion results of Study P-16010 were included in the original NDA. The PK samples were re-analyzed and the analyses were submitted in the resubmission.

Reference: \\CDSESUB1\evsprod\nda212304\0028\m2\25-clin-over\25-clinical-overview.pdf Page 19, Table 6

4. Summary of Pivotal Relative Bioavailability Study (CL-P-20003)

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

Primary Objective: To assess the bioequivalence of steady-state donepezil plasma exposure following once-weekly treatments with the final, to-be-marketed 10 mg/day Donepezil TDS compared to once-daily oral administration of 10 mg ARICEPT.

Second Objective: To assess the bioequivalence of steady-state donepezil plasma exposure (after dose-normalization) following once-weekly treatments with the final, to-be-marketed 5 mg/day Donepezil TDS compared to once-daily oral administration of 10 mg ARICEPT.

Study Design and Methodology:

This is a Phase 1, open-label, randomized (partially), 3-period, 3-treatment, crossover pharmacokinetic study to evaluate the steady-state PK of the to-be-marketed once-weekly 5 mg/day and 10 mg/day ADLARITY Donepezil TDS products compared to 10 mg once-daily oral administration of ARICEPT in healthy volunteers. A total of 60 healthy subjects were enrolled and assigned to receive the 3 treatments. Subjects were 22 females (36.7%) and 38 males (63.3%), 19 years to 55 years old. Most of the subjects were White (93.3%), and about 1/3 were Hispanic or Latino (36.7%).

For safety reasons (to allow subjects to get accustomed to the potential cholinergic effects of donepezil), every subject received the 5 mg/day Donepezil TDS weekly for 5 weeks (one patch once a week) at first (Treatment A, not included in the randomization, during Period 1). During Treatment Periods 2 and 3, subjects received 10 mg/day Donepezil TDS weekly for 5 weeks (Treatment B) or 10 mg/day oral tablets for 5 weeks (one 10 mg Aricept tablet QD) (Treatment C). The subjects were randomized to receive either sequences of Treatments B-C or Treatments C-B in Periods 2 and 3. Randomization to the 2 treatment sequences were stratified by gender. There was no wash-out period between treatments.

PK Sampling: The blood samples were collected for PK analysis to determine the plasma concentrations of both donepezil and 6-O-desmethyl donepezil (active metabolite of donepezil) at the following time frames:

- Treatments A and B (treatment with weekly ADLARITY TDS for 5 weeks):
  - Week 1: Pre TDS#1 application, and at 2, 6, 12, 24, 48, 72, 96, 120, and 144 hours after TDS #1 application.
  - Week 2: Pre TDS#2 application, and at 24, 48, 72, 96, 120, and 144 hours after TDS #2 application.
  - Week 3: Pre-TDS #3 application
  - Week 4: Pre-TDS #4 application
  - Week 5: Pre-TDS #5 application, and at 3, 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156 hours after TDS #5 application.
  - Week 6: Pre-TDS #5 removal (168 hours after TDS #5 application), and at 2, 6, 8, 10, and 12 hours after TDS #5 removal

- Treatment C (oral ARICEPT QD for 35 days):
  - Week 1: Pre-Dose, and at 1, 2, 3, 4, 6, 8, 12 and 24 hours after oral administration
  - Weeks 2, 3, 4: Pre-Dose
  - Week 5: Pre-Dose, and 1, 2, 3, 4, 6, 8, 12 and 24 hours after oral administration

Table 3: Treatments in the Study CL-P-20003

	Treatment A	**Treatment B**	**Treatment C**
Product Administered	ADLARITY 5 mg/day	ADLARITY 10mg/day	ARICEPT Tablets 10 mg
Dosing	One patch once a week	One patch once a week	One tablet QD
Route of Administration	Transdermal	Transdermal	Oral
Other Characteristics	With a light meal 30 minutes before the dose; no water allowed for 1 hour before the dose	With a light meal 30 minutes before the dose; no water allowed for 1 hour before the dose	With a light meal 30 minutes before the dose; no water allowed for 1 hour pre-dose and 1 hour post-dose

PK Analysis Method:

The plasma donepezil concentration data from the 5th week of the treatments were used to compare the steady-state PK of once weekly ADLARITY patch (both 10 mg/day and 5 mg/day TDS) with once-daily ARICEPT tablets. For BE analysis, plasma donepezil exposure as characterized by $AUC_{tau(0\text{-}168h)}$ and C_{max} at Week 5 as well as the C_{trough} (at end of Week 5) was assessed and compared between the TDS and ARICEPT utilizing bioequivalence criteria. The PK data of the TDS 5 mg/day dose were normalized by dose (multiplied by 2 to match 10 mg/day). For ARICEPT oral tablets, only the PK profiles on the last day of the treatment (Treatment C) were available. Therefore, the AUCtau of the last day of oral dose was multiplied by 7 for the BE analyses with the TDS products.

In addition, the dosage strength proportionality was assessed by the reviewer between the tested two strengths of the TDS (5 mg/day and 10 mg/day) based on the BE analysis of the dose-normalized systemic exposure (i.e., C_{max} and AUC_{tau}) of donepezil at steady state.

Number of Subjects (Planned and Analyzed):

There were 60 subjects who received the 5 mg/day Donepezil TDS, 55 subjects who received the 5 mg/day ADLARITY, and 56 subjects who received 10 mg/day oral ARICEPT; 52 subjects received all 3 treatments in the study. Eight subjects were discontinued early from the study and were excluded from the primary BA population,

including: 3 subjects were withdrawn due to protocol non-compliance; 1 subject withdrew consent; 2 subjects were withdrawn by the Investigator; and 2 subjects terminated early for reasons of “other”. There was one subject who experienced early TDS detachment during Week 5 of Treatment A and this subject was excluded for the relative bioavailability comparison for Treatment A with other treatments. No subjects terminated the study early because of adverse events (AEs).

Overall, the PK Population included 56 subjects from Treatment A, 53 subjects from Treatment B, and 53 subjects from Treatment C. The relative bioavailability population included 51 subjects from Treatment A and 52 subjects from Treatments B and C.

PK Results:

Donepezil

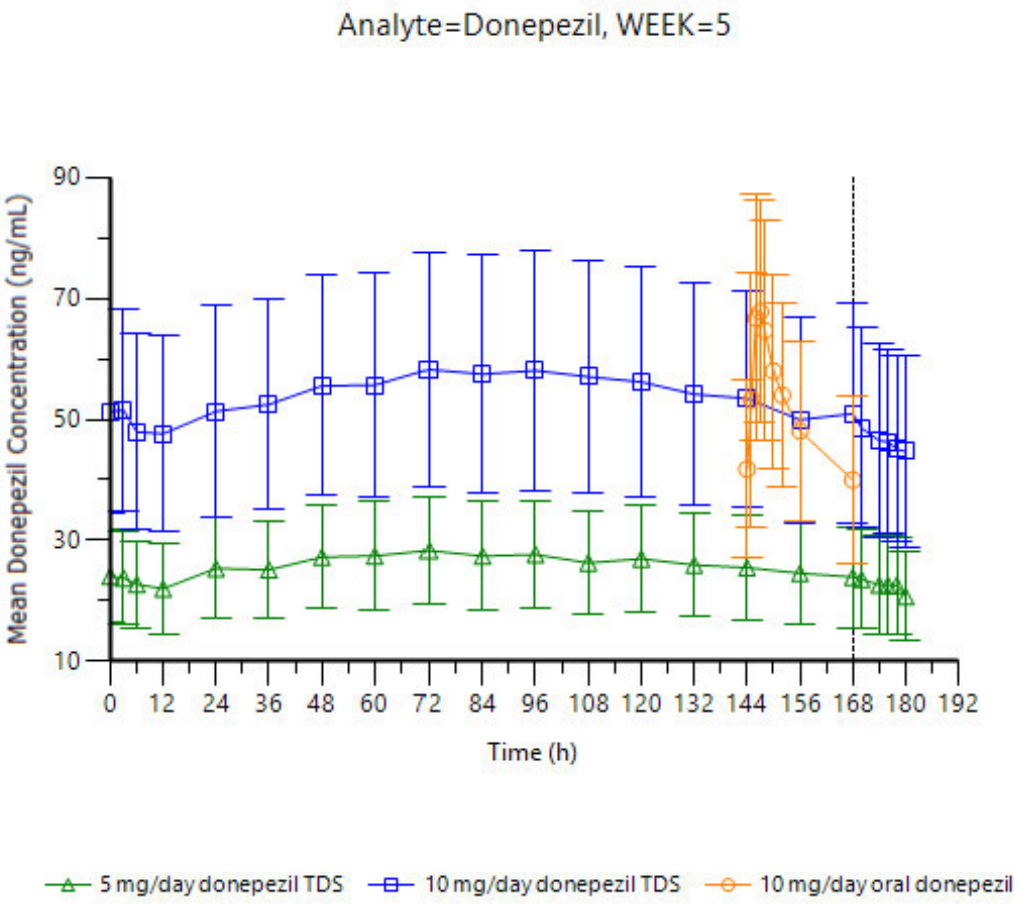
The mean donepezil concentration-time profiles of once weekly ADLARITY patch (both 10 mg/day and 5 mg/day TDS) and once-daily ARICEPT tablets at Week 5 are shown in Figure 1. The mean (±SD) C_{trough} vs time (Weeks 1 through 5) profiles after 5 mg/day and 10 mg/day TDS Application and ARICEPT are presented in Figure 2. The attainment of steady state was confirmed with mixed effect models by comparing donepezil trough levels of each week (C_{trough}) within individual treatment. Based on the results, steady state for donepezil was reached by Day 22 for 5 mg/day and 10 mg/day ADLARITY TDS (Treatment A and B) and by Day 8 for once-daily oral 10 mg ARICEPT (Treatment C).

The least squares geometric means (LSGM) of the PK parameters for each treatment were compared, along with the point estimates of the Test to Reference ratios of geometric means and 90% Confidence Intervals (CIs). The bioequivalence assessment results (reviewer’s analysis) are shown in Tables 4 and 5. Based on the results, the 90% CIs for the donepezil C_{max} and AUC_{tau} at steady state were within the 80% to 125% range for establishing bioequivalence between the ADLARITY TDS 10 mg/day product to the ARICEPT oral tablets 10 mg. For the comparison between the TDS 5 mg/day and the ARICEPT, the 90% CIs for the donepezil AUCtau at steady state meet the BE criteria within the range of 80% to 125%, while the 90% CIs for C_{max} is on the border line of lower bound for BE criteria.

C_{trough} of 10 mg/day TDS Applications at steady state is noninferior compared to that for ARICEPT oral daily dose. The geometric mean ratio of C_{trough} at steady state (TDS:oral) is 1.2 and the 90% CIs was (119-138) Table 4.

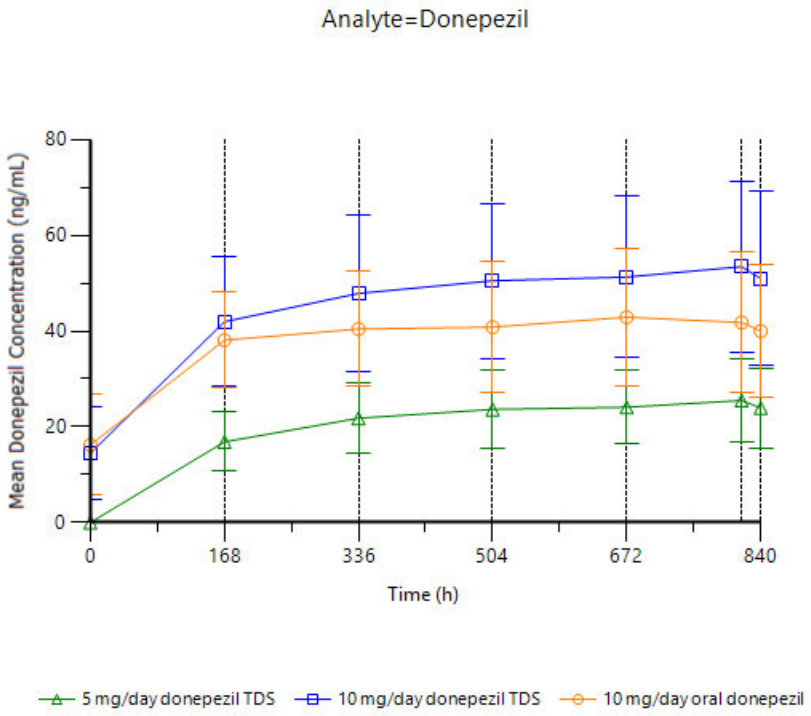
As presented by Table 6, the two strengths of the TDS product showed proportionality based on the BE analysis of systemic exposure of donepezil (dose-normalized).

Figure 1: Mean (±SD) Plasma Donepezil Concentration-Time Data after 5 mg/day and 10 mg/day ADLARITY TDS Application and after 10 mg ARICEPT QD oral administration at steady state (the last week of each treatment) - PK Population



Source: Corium clinical study report CL-P-20003: Figure 1, Page 75

Figure 2: Mean (±SD) Donepezil C_{trough} vs time profiles (Weeks 1 through 5) after 5 mg/day, 10 mg/day TDS Application and ARICEPT 10 mg QD tablets on Linear Scale.



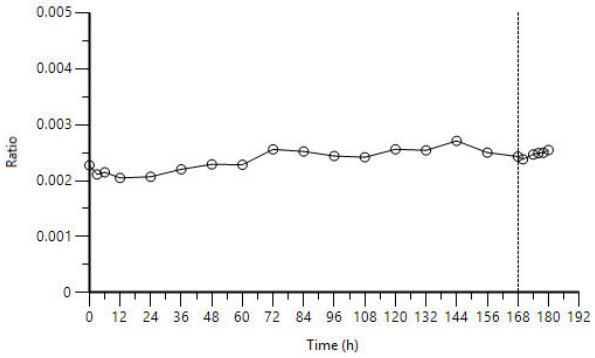
Source: Corium clinical study report CL-P-20003: Figure 2, Page 77

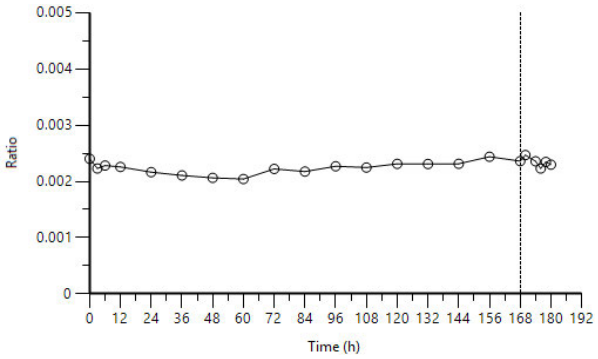
6-O-desmethyl donepezil

For all treatments, 6-O-desmethyl donepezil was determined to be a minor metabolite of donepezil. The mean concentration ratio (metabolite: parent)-time profiles at Week 5 are presented in Figure 3. The Mean concentration ratios of 6-O-desmethyl donepezil to donepezil were generally under 0.003 (i.e., less than 0.3%) on Week 5 across treatments.

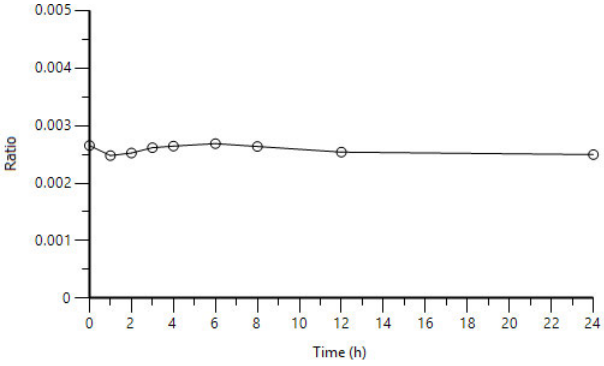
Figure 3: Mean Plasma 6-O-Desmethyl Donepezil to Donepezil Concentration Ratios after A: 5 mg/day TDS, B:10 mg/day TDS, and C:10 mg/day Oral Aricept (Week 5; PK Population)

A: 5 mg/day TDS **B: 10 mg/day TDS**





C: 10 mg/day Oral Aricept



Source: Corium clinical study report CL-P-20003: Figure 6, Page 89

Table 4: Bioequivalence assessment of PK parameters at steady state between ADLARITY TDS 10 mg/day and AIRCEPT 10 mg in Study CL-P-20003 (Reviewer's analysis)

Treatment	n	GeoMean	Comparison	GeoMean Ratio	90% CI lower	90% CI upper
AUCtau (ng*hr/mL)						
B: TDS 10 mg/day	52	8624.98	TDS/Oral Reference:Oral	101.27	99.50	116.61
C: Oral 10 mg	52	8007.87				
Cmax (ng/mL)						
B: TDS 10 mg/day	52	59.13	TDS/Oral	87.86	80.74	95.62

C: Oral 10 mg	52	67.30	Reference:Oral			
Ctrough (ng/mL)						
B: TDS 10 mg/day	52	48.06	TDS/Oral	128.78	119.30	137.54
C: Oral 10 mg	52	37.32	Reference:Oral			

Source: \\CDSESUB1\evsprod\nda212304\0028\m5\datasets\cl-p-20003\analysis\adam\datasets\adpc.xpt

Table 5: Bioequivalence assessment of primary PK parameters at steady-state between ADLARITY TDS 5 mg/day and AIRCEPT 10 mg QD in Study CL-P-20003 (Reviewer's analysis)

Treatment	n	GeoMean	Comparison	GeoMean ratio	90% CI lower	90% CI upper
AUCtau (ng*hr/mL)						
A: TDS 5 mg/day	51	8390.37	TDS/Oral Reference:Oral	105.13	97.46	113.40
C: Oral 10 mg	51	7981.41				
Cmax(ng/mL)						
A: TDS 5 mg/day	51	57.66	TDS/Oral Reference:Oral	86.00	79.60	92.92
C: Oral 10 mg	51	67.04				
Ctrough (ng/mL)						
A: TDS 5 mg/day	51	45.34	TDS/Oral Reference:Oral	121.48	112.54	131.14
C: Oral 10 mg	51	37.32				

Source: \\CDSESUB1\evsprod\nda212304\0028\m5\datasets\cl-p-20003\analysis\adam\datasets\adpc.xpt

Table 6: Evaluation of dosage strength proportionality for ADLARITY TDS 10 mg/day and 5 mg/day at steady state in Study CL-P-20003 (Reviewer's analysis)

Treatment	n	GeoMean	Comparison	GeoMean ratio	90% CI lower	90% CI upper
AUCtau (ng*hr/mL)						
A: TDS 5 mg/day	51	8390.37	TDS 5mg/10mg Reference:10 mg	97.91	92.91	103.65
B: TDS 10 mg/day	51	8569.44				
Cmax(ng/mL)						
A: TDS 5 mg/day	51	57.66	TDS 5mg/10mg Reference:10 mg	98.08	92.21	104.33
B: TDS 10 mg/day	51	58.78				

Source: \\CDSESUB1\evsprod\nda212304\0028\m5\datasets\cl-p-20003\analysis\adam\datasets\adpc.xpt

Discussion and Conclusion

This pivotal relative bioavailability study was designed as a crossover study without wash-out period between treatments. Considering the elimination half-life of about 90 hours for both oral and TDS, the carry-over of the last treatment to the following treatment after 4 weeks is minimal and hence it would not expect to impact the BE assessment at steady state at Week 5. This reviewer conducted independent analysis of the PK data and the reviewer's analysis (Tables 4 and 5) agrees with the Applicant's results of BE assessment. In general, the PK metrics meet the BE criteria between ADLARITY TDS (two strengths) and ARICEPT oral 10 mg at steady state based on AUC_{tau} and C_{max}, except the lower bound of 90% CI of geometric mean ratio of C_{max} between ADLARITY 5 mg/day and ARICEPT is 79.6%. The lower bound of 90% CI for C_{max} geometric mean ratio of ADLARITY 5 mg/day to ARICEPT slightly less than 80% of BE criteria is not considered clinically meaningful. The donepezil PK comparison between ADLARITY TDS 10 mg/day and TDS 5 mg/day also indicates the two strengths of the TDS product are proportional at steady state (Table 6).

Although the shapes of PK profiles obtained from TDS and oral are slightly different, the C_{trough} of TDS Application (10 mg/day) through Week 1 to Week 5 are in general higher than that observed from ARICEPT oral daily 10 mg. At steady state, geometric mean ratios of C_{trough} (ADLARITY: ARICEPT) was showing higher levels for ADLARITY, with the 90% CIs beyond the upper bound of the range of 80-125%. Considering the C_{max} and AUC_{tau} of TDS is comparable with oral and C_{trough} of TDS is higher than oral, the PK shape difference does not expect to result in clinically meaningful difference in the efficacy and safety of ADLARITY TDS relative to ARICEPT tablets. In addition, the long half-life of donepezil and the known mechanism of action of donepezil make the fluctuation and the difference in the shape of the PK profiles between the two products minimal.

To evaluate if there is a difference in the metabolic profiles between the two routes, the level of active metabolite, 6-O-Desmethyl-Donepezil was also measured in the pivotal study. The active metabolite level (6-O-Desmethyl-Donepezil) observed in this pivotal study was very low (<0.3%) relative to donepezil exposure across the treatments. These results agree with those observed for oral tablets and transdermal patches in early clinical pharmacology studies (#P-15007 and P-15081) with a single dose intended for formulation selection. Since the exposure level of this active metabolite is low, the bioequivalence assessment based on the metabolite's PK was not performed across treatments. It is worth noting that this active Met/Parent ratio (< 0.3%) is different from the reported ratio in ARICEPT USPI (20%) based on the radioactivity study[5]. The new

[5] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf

findings regarding the level of 6-O-desmethyl donepezil are included in the ADLARITY label.

Overall, this pivotal study (CL-P-20003)'s results provide an adequate scientific bridge for the proposed to-be-marketed ADLARITY TDS products for both strengths, to rely on the labeling information, including the safety and efficacy, of the LD product, ARICEPT oral tablets.

5. Switching from Oral to TDS

In the proposed label (Section 2.3), the following instruction for switching from Donepezil Tablets or Donepezil ODT to ADLARITY (same with the proposed label for the original NDA) is provided:

Patients treated with donepezil 5 mg or 10 mg tablets may be switched to ADLARITY as follows:

- *A patient who is being treated with a total daily dose of 5 mg of oral donepezil can be switched to the once weekly 5 mg/day ADLARITY TDS. Patients may be switched immediately to the once weekly 10 mg/day transdermal system if the patient has been on 5 mg oral donepezil for at least 4-6 weeks.*

- *A patient who is being treated with a total daily dose of 10 mg of oral donepezil can be switched to the once weekly 10 mg/day ADLARITY TDS.*

Instruct patients or caregivers to apply the first TDS (b) (4).

(b) (4) was evaluated for the original NDA and documented in Section 4.2.4 Pharmacometrics Review of the original Clinical Pharmacology review[6]. Briefly, the PK profiles were simulated using non-parametric superposition for different timing of oral-to-TDS switch for both 10 mg/day and 5 mg/day TDS at steady state, including TDS application at the time of last oral dose (at time 0), 12 hours and 24 hours after oral dose. Based on the simulation results, for both 5 mg/day and 10 mg/day TDS treatments, donepezil concentrations during the first 10 days after oral-to-TDS switch were lower than the $C_{min,ss}$ of oral treatment at steady state. The findings were communicated to the applicant in the Complete Response letter dated July 23, 2020, which recommended further analyses to derive an appropriate oral-to-TDS switching strategy, e.g., the need of oral supplementation for oral-to-TDS switch in the first 10 days.[7]

For this resubmission, the applicant (b) (4). To identify an optimal oral-to-TDS switching strategy, additional simulations

[6] Clinical pharmacology review in DARRTS Dated 5/28/2020 Page 31

[7] Complete Response Letter documented in DARRTS dated 7/23/2020, Page 7

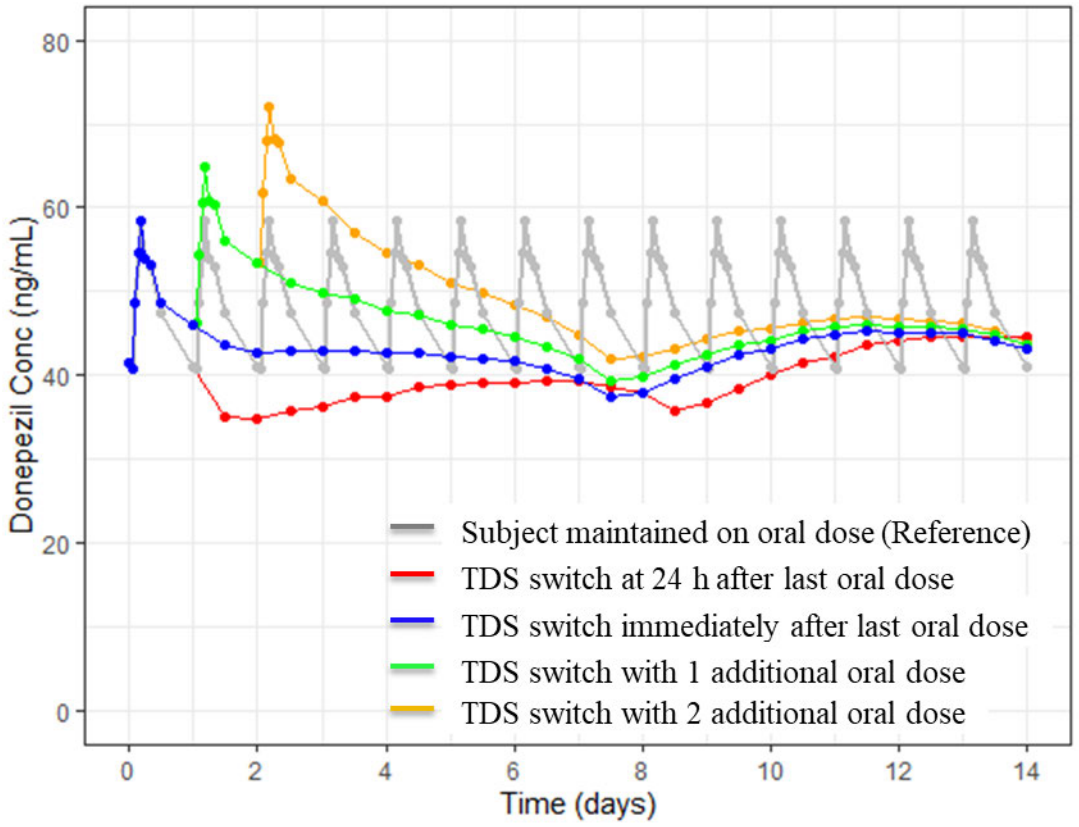
were performed by the pharmacometrics reviewer, Dr. Vishnu D. Sharma. Briefly, for the switching from oral 10 mg QD at steady state to the TDS 10 mg/day, PK profiles were simulated for various scenarios including:

1) Scenario 1: oral-to-TDS switch at 24 h after last oral dose
2) Scenario 2: oral-to-TDS switch immediately after the last oral dose (
3) Scenario 3: oral-to-TDS switch immediately after the last oral dose and followed by 1 additional oral dose after 24 hours
4) Scenario 4: oral-to-TDS switch immediately after the last oral dose followed by 2 additional oral doses (one tablet every 24 hours)

The PK profiles from all the scenarios are presented in Figure 4. The results indicate that the donepezil concentrations in Scenario 1 was lower than oral $C_{min,ss}$ for first 10 days after the oral-to-TDS switch, while the donepezil exposure in Scenario 4 was higher than oral $C_{max,ss}$ by 23%. The plasma donepezil levels from Scenario 2 was within the oral $C_{max,ss}$-$C_{min,ss}$ range of the oral dose.

Since the two strengths of TDS (5 mg/day and 10 mg/day) are dose proportional, similar PK results would be expected for the oral-to-TDS switch of 5 mg/day regimen. Based on results, the review team supported that Scenario 2 would have more patient compliance and less prone to medication error. The following recommendations were made in the label Section 2.2: “Instruct patients or caregivers to apply the first transdermal system with the last administered oral dose”.

Figure 4: Simulated PK profiles of donepezil for various scenarios to evaluate the switch from oral donepezil 10 mg/day at steady state to 10 mg/day ADLARITY TDS patch (Reviewer's assessment)



Source: Reviewer's analysis

6. Summary of other Clinical Pharmacology Assessments

6.1 Summary of Clinical Pharmacology Assessment for the original NDA

The general pharmacology and pharmacokinetic characteristics of ADLARITY were summarized in Section 3.2 in the Clinical pharmacology review for the original NDA[8]. Highlights of previous assessments are provided below:

- Dose proportionality was established from ADLARITY TDS 50 cm^2 to ADLARITY TDS 105 cm^2 using power model assessment.
- The effect of TDS application site was evaluated in Study P-16012. Mean exposure (AUC_{inf} and C_{max}) following TDS application to the thigh was 14% to 18% lower than to the back, whereas following TDS application to the buttock, exposure was 21% to 24% higher than to the back. Since the PK obtained from the three application locations did not meet the BE criteria and the back was the only

[8] Clinical pharmacology review in DARRTS Dated 5/28/2020 Page 8

application site in the pivotal studies, it recommended that Donepezil TDS should be applied to the back only.

- Based on the Study P-16039 which evaluated the effect of heat exposure of TDS on the donepezil PK, transitory increases (up to 60% increase in the partial AUC according to the heat application periods) was observed during heat sessions compared with control conditions. “Avoid applying heat” or a similar statement was recommended to be included in the label.

Please refer to the clinical pharmacology review documented in DARRTS dated 5/28/2020[1] for details of the assessment.

6.2 Highlight of Results from other Clinical Studies Included in the Resubmission

The clinical studies submitted in this resubmission are listed in Table 2. The assessment of the pivotal relative BA study (#CL-P-20003) is included in Section 4. The other two new studies (Study CL-P-20004 and Study CL-P-19005) along with the PK data re-analysis for Study P-16010 are mainly to address the quality concerns included in the CRL (see Table 2 for the description of the studies).

Study CL-P-20004 was conducted primarily to support shelf-life, which is a single-dose and crossover PK study comparing the (b) (4) donepezil TDS 5 mg/day stored for about 24 months at 2-8°C to the to-be-marketed (b) (4) TDS 5 mg/day stored for about 24 months at 2-8°C. Study CL-P-19005 was conducted to assess the relative bioavailability of the TDS products 10 mg/day between the patches without crystal and with crystals represented patches (that contained crystals covering (b) (4)% of the active delivery area of the patch), using the previous to-be-marketed TDS without (b) (4). Study P-16010 was conducted during October 2017 and March 2018 mainly to support the safety and adhesion for the (b) (4) TDS patches (previous to-be-market) product 10 mg/day compared to daily oral ARICEPT administration (10 mg, QD). The PK samples were analyzed, and the results are submitted in this resubmission. The submitted results in all these studies indicates bioequivalence was established between the studied treatments in individual studies. As these studies are not essential for this NDA approval, the study details are not assessed by this reviewer. For the shelf life and crystal content specifications, please refer to the assessment of CMC and Biopharmaceutics.

7. Appendix

Summary of Bioanalytical Method Validation and Performance

The validated LC/MS/MS method (Method 2, BAM SOP ZZ49214-01) for the determination of donepezil in human plasma was used for the new studies included in

this resubmission (Studies # CL-P-20003, CL-P-20004, CL-P-19005) as well as Study P-16010. The method was evaluated in the original review by Clinical Pharmacology reviewer Dr. Hristina Dimova and concluded adequate[9]. The sample analysis for the pivotal relative bioavailability study (Study # CL-P-20003) are reviewed by this reviewer and considered adequate.

A new LC/MS/MS method (Method 3, BAM SOP ZZ49214-03) for the determination of the metabolite, 6-O-desmethyl donepezil, in human plasma was development for Study CL-P-20003. Method 3 is only for the assay of 6-O-desmethyl donepezil, different from the previously validated method Method 1 for the determination of both 6-O-desmethyl donepezil and donepezil (previous evaluated and conclude adequate). Method 3 was validated for quantitation of donepezil in human plasma over the concentration range of 10 pg/mL to 2000 pg/mL. The validation summary and sample analysis are adequate.

Table 7: Validation Summary for Method 3 (Study ZZ49214-03)

[9] Clinical pharmacology review in DARRTS Dated 5/28/2020 Page 21

Validation Summary – 6-O-Desmethyl Donepezil	
Validation Study Number	[redacted] (b) (4). Validation Study ZZ49214-03
Bioanalytical Method (BAM) SOP Number	BAM SOP ZZ49214-03 (Attachment 2)
Analyte	6-O-Desmethyl Donepezil
Internal Standard (IS)	d_5-6-O-Desmethyl Donepezil
Matrix	Human Plasma
Anticoagulant	K_2EDTA
Assay Volume Required	0.100 mL
Regression Type	Weighted linear (1/concentration^2) (Section 2.2, Table 4, and Table 6)
Quantitation Method	Peak area ratio
Method Description	Liquid-liquid extraction with analysis/detection by LC-MS/MS (Section 1.1.2)
Detector	AB SCIEX Triple Quad™ 6500 (Section 1.1.3)
Limit of Quantitation (pg/mL)	10.0 pg/mL (Section 2.4.1 and Table 2)
Standard Curve Concentrations (pg/mL)	10.0, 20.0, 50.0, 100, 250, 500, 750, 1600, and 2000 pg/mL
QC Concentrations (pg/mL)	10.0 (LLOQ QC), 30.0 (Low), 140 (Medium Low), 600 (Medium High), 1500 (High), and 5000 (Dilution QC) pg/mL
Average Recovery of Drug (% Mean)	105% at 30.0 pg/mL 105% at 140 pg/mL 98% at 1500 pg/mL (Section 2.5 and Table 17)
Average Recovery of IS (% Mean)	104% (Section 2.5 and Table 18)
QC Within-Run Precision Range (% CV)	0.9 to 4.0% (Table 2)
QC Within-Run Accuracy Range (% Bias)	4.0 to 11.3% (Table 2)
QC Between-Run Precision Range (% CV)	1.8 to 3.9% (Table 2)
QC Between-Run Accuracy Range (% Bias)	5.3 to 8.7% (Table 2)

Validation Summary – 6-O-Desmethyl Donepezil			
Quality Control Samples (Table 2)		**Precision (% CV)**	**Accuracy (% Bias)**
Between-Run	**LLOQ** **Low** **Medium** **High**	3.9 3.0 2.2 1.8 2.4	7.0 7.7 5.7 5.3 8.7
Within-Run (Run 31)	**LLOQ** **Low** **Medium** **High**	3.0 1.3 2.1 1.0 1.8	10.0 7.3 4.3 4.0 6.7
Within-Run (Run 33)	**LLOQ** **Low** **Medium** **High**	3.1 1.5 1.2 0.9 1.5	6.0 5.0 5.0 4.7 7.3
Within-Run (Run 35)	**LLOQ** **Low** **Medium** **High**	4.0 2.4 1.5 1.6 2.2	4.0 11.3 7.9 7.2 10.7
Selectivity		No significant interference at the retention time and mass transition of 6-O-desmethyl donepezil was observed from endogenous components in 9 of the 10 human plasma (EDTA) lots screened or of d_5-6-O-desmethyl donepezil (IS) in 10 of the 10 human plasma (EDTA) lots screened (Section 2.4.2 and Table 9)	
Matrix Effect		No significant matrix effect was observed in 10 of the 10 human plasma (EDTA) lots which were spiked with 6-O-desmethyl donepezil at the concentration of the low QC (30.0 pg/mL) or in 10 of the 10 human plasma (EDTA) lots which were spiked with 6-O-desmethyl donepezil at the concentration of the high QC (1500 pg/mL) samples (Section 2.4.3 and Table 10)	

Validation Summary – 6-O-Desmethyl Donepezil	
Over-the-Counter Cocktail Testing	Acetaminophen (25.0 µg/mL) Atorvastatin (100 ng/mL) Caffeine (20.0 µg/mL) Cetirizine (500 ng/mL) Cotinine (250 ng/mL) Dextrorphan (5000 ng/mL) Ethinyl Estradiol (0.500 ng/mL) Famotidine (200 ng/mL) Ibuprofen (20.0 µg/mL) Metformin (2.00 µg/mL) Norethindrone (10.0 ng/mL) Omeprazole (300 ng/mL) Pseudoephedrine (500 ng/mL) Salicylic Acid (100 µg/mL) (Section 2.4.5 and Table 13)
Selectivity from Known Metabolites	At the High QC Concentration: Donepezil (150,000 pg/mL) 5-O-Desmethyl Donepezil (15,000 pg/mL) At the Low QC Concentration: Donepezil (3000 pg/mL) 5-O-Desmethyl Donepezil (300 pg/mL) (Section 2.4.6 and Table 14)
Hemolyzed Sample Integrity	No significant interference for 6-O-desmethyl donepezil was observed in 3 of 3 replicates from 1 hemolyzed human plasma (EDTA) lot (fortified with 2% whole blood) which was spiked at the concentration of the low QC (30.0 pg/mL) or in 3 of 3 replicates from 1 hemolyzed human plasma (EDTA) lot (fortified with 2% whole blood) which was spiked at the concentration of the high QC (1500 pg/mL) (Section 2.4.7 and Table 15)
Lipemic Sample Evaluation	No significant interference for 6-O-desmethyl donepezil was observed in 3 of 3 replicates from 1 lipemic human plasma (EDTA) lot which was spiked at the concentration of the low QC (30.0 pg/mL) or in 3 of 3 replicates from 1 lipemic human plasma (EDTA) lot which was spiked at the concentration of the high QC (1500 pg/mL) (Section 2.4.8 and Table 16)
Sample Shipping Stability	6 days in polypropylene tubes at -80°C (Section 2.6.1 and Table 19)
Long-Term (Frozen) Storage Stability in Matrix	105 days in polypropylene tubes at -20°C (Section 2.6.2 and Table 20)

Validation Summary – 6-O-Desmethyl Donepezil	
Freeze-Thaw Stability in Matrix	6 freeze (-20°C)-thaw (at ambient temperature) cycles in polypropylene tubes under white light (Section 2.6.3 and Table 21)
Short-Term (Bench-Top) Stability in Matrix	Short-Term Stability: 25 hours in polypropylene tubes at ambient temperature under white light Cumulative Short-Term Stability: 52 hours in polypropylene tubes at ambient temperature under white light (total of all thaw cycles) (Section 2.6.3 and Table 21)
Processed Stability	Processed Sample Stability (Extract Stability): 80 hours in a polypropylene 96 well plate at 5°C (Section 2.6.4 and Table 22) Processed Sample Integrity (Autosampler Stability): 198 hours in a polypropylene 96 well plate at 5°C (Section 2.7.2 and Table 35)
Long-Term Stability for Stock Solutions (Stock)	171 days at approximately 1000 µg/mL in methanol in a polypropylene container at -20°C (Section 2.6.5 and Table 23)
Long-Term Stability for Stock Solutions (Substock)	61 days at 100 µg/mL in methanol in a polypropylene container at -20°C 14 days at 1.00 ng/mL in methanol in a polypropylene container at -20°C (Section 2.6.5, Table 24, and Table 25)
Long-Term Stability for Stock Solutions (Internal Standard)	Refer to long-term stability for stock solutions data collected from unlabeled 6-O-desmethyl donepezil for labeled internal standard stability (Section 2.6.5)
Short-Term Stability for Stock Solutions (Stock)	6 hours at approximately 1000 µg/mL in methanol in a polypropylene container at ambient temperature under white light (Section 2.6.6 and Table 26)
Short-Term Stability for Stock Solutions (Substock)	6 hours at 100 µg/mL in methanol in a polypropylene container at ambient temperature under white light 6 hours at 1.00 ng/mL in methanol in a polypropylene container at ambient temperature under white light (Section 2.6.6, Table 27, and Table 28)
Short-Term Stability for Stock Solutions (Internal Standard Stock)	Refer to short-term stability for stock solutions data collected from unlabeled 6-O-desmethyl donepezil for labeled internal standard stability (Section 2.6.6)

Validation Summary – 6-O-Desmethyl Donepezil	
Short-Term Stability for Stock Solutions (Internal Standard Substock)	6 hours at 750 pg/mL in methanol in a polypropylene container at ambient temperature under white light (Section 2.6.6 and Table 29)
Stability of Analyte During Sample Collection and Handling	Up to 120 minutes in human whole blood (EDTA) in polypropylene tubes at ambient temperature under white light[1] (Section 2.6.7 and Table 30)
Sample Aliquot Frozen Storage Stability	Samples aliquoted manually at a volume of 0.100 mL, stored for 142 hours in a polypropylene 96 well plate at -20°C, and then thawed at ambient temperature under UV-shielded light prior to extraction (Section 2.6.8 and Table 31)
Known Metabolite Long-Term (Frozen) Stability in Matrix	Against Donepezil and 5-O-Desmethyl Donepezil: 18 days in polypropylene tubes at -20°C (Section 2.6.9.1 and Table 32)
Known Metabolite Freeze-Thaw Stability in Matrix	Against Donepezil and 5-O-Desmethyl Donepezil: 6 freeze (-20°C)-thaw (at ambient temperature) cycles in polypropylene tubes under white light (Section 2.6.9.2 and Table 33)
Known Metabolite Short-Term (Bench-Top) Stability in Matrix	Known Metabolite Short-Term Stability Against Donepezil and 5-O-Desmethyl Donepezil: 25 hours in polypropylene tubes at ambient temperature under white light Known Metabolite Cumulative Short-Term Stability Against Donepezil and 5-O-Desmethyl Donepezil: 52 hours in polypropylene tubes at ambient temperature under white light (total of all thaw cycles) (Section 2.6.9.2 and Table 33)
Dilution Integrity	5000 pg/mL samples diluted up to 20-fold can be quantified (Section 2.7.1 and Table 34)
Run Size	192 injections

Source: Report for (b) (4) Validation Study ZZ49214-03

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MIN LI
03/04/2022 03:16:27 PM

VISHNU D SHARMA
03/04/2022 05:22:06 PM

VENKATESH A BHATTARAM
03/04/2022 07:05:56 PM

BILAL S ABU ASAL
03/07/2022 10:50:59 AM

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	212304
Submission Date	Sept 30, 2019
Submission Type	505(b)(2) NDA
Brand Name	ADLARITY
Generic Name	Corplex Donepezil transdermal delivery system (TDS)
Dosage Form and Strength	transdermal delivery system, 52.5 cm^2 and 105 cm^2
Route of Administration	transdermal
Proposed Indication	Symptomatic treatment of mild, moderate and severe Alzheimer's Disease (AD)
Applicant	Corium
OCP Review Team	Hristina Dimova, Vishnu Sharma, Angela Men, Atul Bhattaram

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

ADLARITY is a once-weekly Transdermal Delivery System (TDS) that is designed to continuously deliver 5 mg/day or 10 mg/day of donepezil for 7 days (l week). This is a 505(b)(2) NDA to reference Aricept® (NDA 020690) as the listed drug (LD). Two strengths of the Donepezil TDS are proposed for marketing: 52.5 cm2 (intended to deliver 5 mg/day); and 105 cm2 (intended to deliver 10 mg/day).

No efficacy studies have been conducted with this product. As agreed, Donepezil TDS efficacy is based on pharmacokinetic (PK) bridging approach. Study P-15086 was conducted to establish bioequivalence (BE) of Donepezil TDS with donepezil (Aricept®) tablets.

Additionally, this NDA is supported by the following clinical pharmacology studies:

• P-16010, safety/adhesion study (PK samples were collected but not analyzed in this study),

• P-16011, skin irritation and sensitization study,

• P-16012, comparative study for bioavailability after application at different body locations,

• P-16039, effect of heat on donepezil delivery profile,

• Studies P-15007, P-15081, and P-16007: early clinical pharmacology studies intended to identify a formulation of this product for further clinical development.

BE was established at steady state between Once-Weekly Donepezil TDS and Aricept®. Both $C_{max,ss}$ and $AUC_{0\text{-}tau}$ met the statistical criteria for BE in the pivotal study P-15086 over the one-week dosing interval. However, the manufacturing process used for the product that was used in study P-15086 is not the same as the proposed manufacturing process for the commercial product. Per OPQ, the changes in manufacturing process are significant enough that a PK bridge needed (i.e. the in vitro methods show a change that cannot be sufficiently explained due to confounding factors). Several additional OPQ issues preclude approval of this NDA in this review cycle, refer to the Discipline Review Letter (DRL).

A consult was sent to the Office of Scientific Inspections and Surveillance (OSIS) requesting clinical and bioanalytical site inspections for BE study P-15086. OSIS determined that inspections are not warranted at this time as these sites were recently inspected (DARRTS 05/07/2020).

1.1 Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 212304 and finds it not acceptable from an OCP perspective. Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	BE was established at steady state between Donepezil TDS and the LD Aricept® in the pivotal study P-15086 over the one-week dosing interval. However, the manufacturing process used for the product in study P-15086 is not the same as the proposed manufacturing process for the commercial product. Per OPQ, the changes in manufacturing process are significant. An additional PK bridge is needed between the product that was used for study 15086 and the commercial product (i.e. the product used for studies 16010, 16012). Several additional OPQ issues preclude approval of this NDA in this review cycle, refer to the Discipline Review Letter (DRL).
General dosing instructions	This is premature. Refer to Section 3.3.1.
Dosing in patient subgroups (intrinsic and extrinsic factors)	ADLARITY should be applied to the back only. Avoid applying heat.
Labeling	This is premature. Refer to Section 3.3.1.
Bridge between the to-be-marketed and clinical trial formulations	The manufacturing process used for the product used in the "pivotal" study P-15086 is not the same as the proposed manufacturing process for the commercial product. An additional PK bridging information is needed between the product that was used for study P-15086 and the commercial product.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

ADLARITY is a once-weekly TDS designed to continuously deliver 5 mg/day or 10 mg/day of donepezil for 7 days (l week) and is indicated for the symptomatic treatment of mild, moderate and severe Alzheimer's dementia.

Donepezil hydrochloride (the active ingredient in both ADLARITY and ARICEPT) is a reversible inhibitor of the enzyme acetylcholinesterase (AChE). Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.

2.1.1 Pharmacokinetic Comparison between ADLARITY and ARICEPT

Bioequivalence was established at steady state between Once-Weekly Donepezil TDS and the LD Aricept®. Both $C_{max,ss}$ and $AUC_{0\text{-}tau}$ met the statistical criteria for BE in the "pivotal" study P-15086 over the one-week dosing interval. However, the manufacturing process used for the

product in study P-15086 is not the same as the proposed manufacturing process for the commercial product. This change in the manufacturing process is significant enough that an additional PK bridge needed (refer to Section 3.3.1 for further details). Therefore, an in vivo PK bridging study is needed between the product that was used for 15086 and the commercial product (i.e. the product used for studies 16010, 16012). PK data from these studies, if appropriate, could be used as the additional PK bridge between the two manufacturing processes.

2.1.2 Dose proportionality between ADLARITY TDS 105 cm² and ADLARITY TDS 50 cm²

Dose proportionality was established from ADLARITY TDS 50 cm^2 to ADLARITY 130 cm^2 including ADLARITY TDS 105 cm^2 using power model assessment (refer to 4.2 Pharmacometrics Review).

2.1.3 Switching to ADLARITY from Donepezil Tablets or Donepezil ODT

Patients treated with donepezil 5 mg or 10 mg tablets may be switched to ADLARITY:

- A patient who is being treated with a total daily dose of 10 mg of oral donepezil can be switched to the once-weekly 10 mg/day ADLARITY patch (b) (4) the last oral dose.
- A patient who is being treated with a total daily dose of 5 mg of oral donepezil can be switched to the once-weekly 5 mg/day ADLARITY patch (b) (4) .

Refer to 4.2 Pharmacometrics Review for further details.

2.2 Dosing and Therapeutic Individualization

This is premature to determine the dosing regimen for ADLARITY. It will depend on the additional PK bridging results. Refer to Section 3.3.1.

Corplex Donepezil TDS should be applied to the back only.

Avoid applying heat.

2.3 Post-Marketing Commitment

None is identified.

2.4 Summary of Labeling Recommendations

This is premature. It will depend on the additional PK bridging study results. Refer to Section 3.3.1.

Corplex Donepezil TDS should be applied to the back only.

Avoid applying heat.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Corplex Donepezil TDS is a once weekly transdermal patch, indicated for the symptomatic treatment of mild, moderate and severe Alzheimer's dementia. This is a 505(b)(2) application with reliance on the FDA's previous finding of the safety and effectiveness of Aricept® (NDA 020690) as the LD. Two strengths of the Donepezil TDS are proposed for marketing: 52.5 cm^2 (intended to deliver 5 mg/day); and 105 cm^2 (intended to deliver 10 mg/day).

The following Clinical Pharmacology related agreements were reached during the Corplex Donepezil TDS Program:

Clinical Topics	Agreements	Reference
Acceptability of justification for omitting metabolite evaluation	FDA agreed to the justification of not conducting further evaluation of the donepezil metabolites in the development program based on preliminary data from early stage Phase 1 Australian studies showing active metabolite (6-O-desmethyl donepezil) exposure relative to parent < 1% and similar in TDS and oral routes	Pre-IND Written Responses 28 April 2016 (Question 15)
Acceptability of Pilot Study P-15086 as the pivotal bioequivalence (BE) study	FDA stated that a preliminary review of the study report for Study P-15086 indicated that the study may be sufficient as the sole basis for demonstrating BE to support the NDA. The acceptability of BE proposal in lieu of clinical efficacy studies was previously agreed in pre-IND written responses dated 28 April 2016	EOP2 Meeting Minutes 22 September 2017 (Question 15) FDA email communication 20 February 2018 - Report for Pilot BE study (P-15086) – Clin Pharm Response*
Demonstration of dose proportionality	FDA accepted the Sponsor methodology for demonstrating dose proportionality in the BE study P-15086, and therefore a separate dose proportionality study would not be required.	EOP2 Meeting Minutes 22 September 2017 (Question 19)
[redacted] (b) (4)		EOP2 Meeting Minutes 22 September 2017 (Question 20)
P-15086 study design: adhesion assessment	FDA agreed that the design of the BE study, P-15086, supports the assessment of adhesion of the product (size and formulation) used in that investigation.	EOP2 Meeting Minutes 22 September 2017 (Question 21)
Comparative bioavailability of patch applied at different body locations study design	FDA agreed to the proposed study design of P-16012 to evaluate comparative bioavailability of patches applied at different body locations	EOP2 Meeting Minutes 22 September 2017 (Question 25)
Effect of heat on delivery profile	FDA requested the Sponsor to investigate the effect of heat on delivery profile of drug product	EOP2 Meeting Minutes 22 September 2017 (Question 31)

Data from the pilot studies P-15007 and P-15081 demonstrated that that 6-O-desmethyl donepezil metabolite exposure relative to parent is < 1% and is similar in TDS and oral routes, refer to Section 4.1 for details. Therefore, BE was based on parent drug (donepezil) only.

The steady state PK of Corplex Donepezil TDS 10 mg/day (105 cm^2) was compared to Aricept 10 mg oral tablets in Study P-15086, and was shown to be bioequivalent in maximum observed plasma concentration at steady state ($C_{max,ss}$) and area under the concentration time curve at steady state (AUC_{ss}) PK parameters. [redacted] (b) (4) However, the manufacturing process for the patch used in the "pivotal" study 15086 is not the same as the proposed manufacturing process for the commercial product. This change in the manufacturing process is significant enough that an additional PK bridge is needed between the product used in 15086 and the commercial product (i.e. the process used for studies 16010, 16012). PK data from these studies, if appropriate, could be the additional in vivo PK bridging study between the products produced from two manufacturing processes. Please refer to Section 3.3.1 for additional details.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Donepezil hydrochloride (the active ingredient in both ADLARITY and ARICEPT) is a reversible inhibitor of the enzyme acetylcholinesterase (AChE). Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.
General Information	
Bioanalysis	Concentrations of donepezil in the main clinical pharmacology studies were measured by validated bioanalytical methods in plasma (Method 2). OSIS determined that bioanalytical site inspection for BE study P-15086 is not warranted at this time. In addition, donepezil and its metabolite 6-O-desmethyl donepezil were quantified using another validated bioanalytical method (Method 1) in the pilot studies P-15007 and P-15081.
Healthy Volunteers vs Patients	NA All clinical pharmacology studies were conducted in healthy subjects.
ADME	
Absorption	In a multiple-dose, crossover clinical study conducted in 60 healthy subjects, donepezil steady state exposure (AUCss) and maximum donepezil concentration at steady state (Cmax,ss), following transdermal administration of once weekly ADLARITY 10 mg/day (applied to the back) were similar to those following daily oral administration of 10 mg donepezil tablets. Donepezil exposure (AUC∞ and Cmax) was 14-18% lower, and 21-24% higher, when the patch was applied on the thigh and buttocks, respectively, when compared to application on the back. ADLARITY should be applied to the back only (the site used in the Pivotal Study).
Distribution	The steady state volume of distribution of donepezil is 12-16 L/kg. Donepezil is approximately 96% bound to human plasma proteins.
Metabolism	Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Notes: Per the ARICEPT label, the major metabolite 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro, was found in plasma at concentrations equal to about 20% of donepezil. However, data from the pilot studies P-15007 and P-15081 demonstrated that that 6-O-desmethyl donepezil metabolite exposure relative to parent is < 1% and is similar in TDS and oral routes.

	Comment: [redacted] (b) (4) ADLARITY labeling language should reflect the new findings from the pilot studies.
Elimination	[redacted] (b) (4) Donepezil is both excreted in the urine intact and metabolized.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

No efficacy studies were conducted for ADLARITY. The evidence of effectiveness relies on the PK bridging between ADLARITY and the LD, ARICEPT. BE of Donepezil TDS with ARICEPT tablets was established at steady state in Study P-15086.

P-15086 was an open-label, randomized, 3-way cross-over, multiple dose study. 60 healthy volunteers were divided evenly into 3 treatments, within 3 treatment Periods, and across 6 treatment sequences. Each treatment period was of 8 weeks duration (comprising 1-week lead-in, 4-week main treatment, and 3-week washout).

• Treatment A (TDS A): 1-week lead-in of once-weekly TDS 5 mg/day (surface area (SA) 50 cm^2) followed by once-weekly TDS A 10 mg/day (SA, 105 cm2) for 4 weeks.

• Treatment B (TDS B): 1-week lead-in of once-weekly TDS 5 mg/day (SA, 50 cm^2) followed by once-weekly TDS B 10 mg/day (SA, 130 cm^2) for 4 weeks.

• Treatment C (Aricept 10 mg or oral C): 1-week lead-in of oral Aricept 5 mg QD followed by oral Aricept 10 mg daily consecutively for 4 weeks.

Each TDS treatment was applied to intact dry skin on the subject's back for 7 days.

Week	Treatment A and Treatment B	Treatment C
1 to 2	Lead-in: from pre-application to 168 h post-application	Lead-in Aricept 5 mg Tablet QD: from pre-dose to 24 h post-dose (Day 1 of Wk 1)
5	Pre-application to 168 h post-application	Pre-dose to 24 h post-dose (Day 7 of Wk 5)
6 to 8	Continuation of sampling to 432 h	Continuation of sampling to 432 h
Trough	Wk 3 (Day 15), Wk 4 (Day 22), Wk 5 (Day 29), Wk 6 (Day 36)	Wk 3 (Day 15), Wk 4 (Day 22), Wk 5 (Day 29), Wk 6 (Day 36)

Abbreviations: A = Donepezil TDS 105 cm^2; B = Donepezil TDS 130 cm^2; C = Aricept 10 mg, h = hour; TDS = Transdermal Delivery System; Wk = Study Week.

Study P-15086 results:

Fifty-one (51) subjects received all three treatments in the study, 10 subjects withdrew/missed treatment from the study, 3 subjects withdrew due to adverse events, 6 withdrew for personal reasons and 1 missed Treatment A due to personal reasons.

Comments: Two subjects reported AEs while receiving Aricept 10 mg: cholecystitis (considered not related to study drug) and non-serious TEAE of atrial fibrillation. A third subject ([redacted] (b) (6)) reported chest pain while receiving donepezil TDS B during Period 1. No evidence of ischemia was found, however as the event was assessed as severe in intensity, and possibly related to the study drug. Per the sponsor, the relationship may possibly have been due to an undiagnosed underlying cardiac abnormality. This AE needs to be further assessed by the clinical team. However, the AE occurred with TDS B (130 cm2 surface area), which provides higher donepezil exposure ($AUC_{0\text{-}168,ss}$) than the proposed TDS A (105 cm2 surface area).

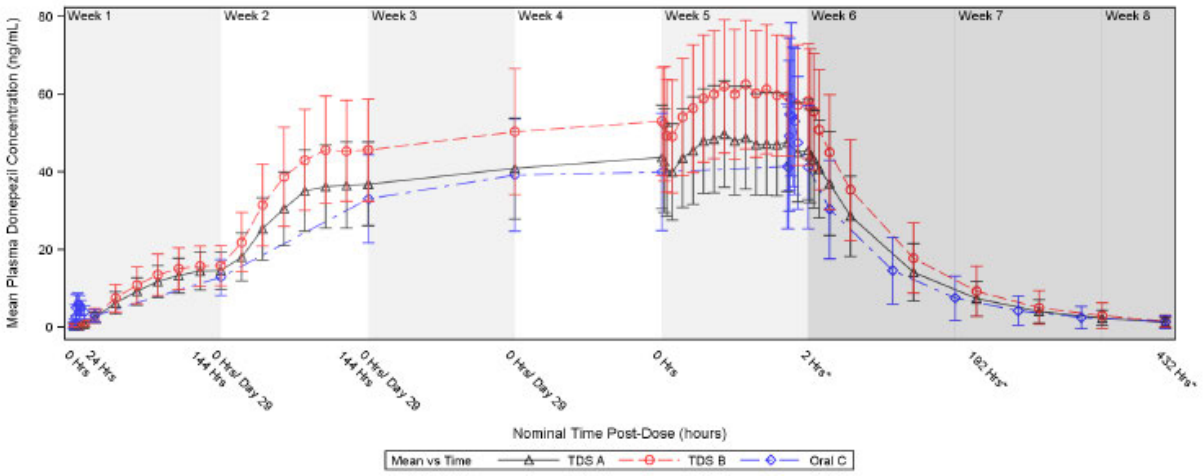
Each treatment period in this study was 5 weeks in duration, with a first-week lead-in period (during which either the Corplex Donepezil TDS in a dose of 5 mg/day or Aricept 5 mg once daily was administered) followed by 4 consecutive weeks during which either once-weekly Corplex Donepezil TDS 10mg/day or Aricept 10 mg once daily was administered; and the bioequivalence assessment was performed during Week 5 of the treatment period (i.e., the fourth week of treatment at the 10 mg/day dose of each formulation).

Attainment of Steady State:

Steady state was achieved by Day 29 (the beginning of steady-state Week 5) for Aricept and was within 5% of steady-state for TDS A (the bioequivalent patch) at that time based on trough levels of interest on Days 15, 22, 29 and 36.

Following four weeks of dosing at 10 mg donepezil/day, higher average plasma donepezil concentrations were observed following administration of TDS B (130 cm^2 surface area) compared to both TDS A (105 cm^2 surface area) and Aricept 10 mg.

Mean (± SD) Plasma Donepezil Concentration vs Time: Entire Profile – PK Population



Bioequivalence Assessment of Primary PK Parameters at Steady-State

Treatment	n	Adjusted Geometric Mean	Comparison	Adjusted GMR	90% CI [a,b]
$AUC_{0-168,ss}$ (ng*h/mL)					
TDS A	52	7685.6	TDS A /Aricept 10 mg	1.047	(0.952, 1.151)
Aricept 10 mg	54	7342.2			
TDS B	52	9392.3	TDS B /Aricept 10 mg	1.279	(1.166, 1.403)
Aricept 10 mg	54	7342.2			
$C_{max,ss}$ (ng/mL)					
TDS A	52	51.464	TDS A /Aricept 10 mg	0.914	(0.830, 1.006)
Aricept 10 mg	54	56.321			
TDS B	52	63.092	TDS B /Aricept 10 mg	1.120	(1.020, 1.230)
Aricept 10 mg	54	56.321			

Abbreviations: A = Donepezil TDS 105 cm^2; B = Donepezil TDS 130 cm^2; C = Aricept 10 mg; CI = confidence interval; adjusted geometric mean = exponentiated least squares mean of the natural log transformed values; GMR = geometric mean ratio; n = number of subjects included in the analysis; TDS = Transdermal Delivery System.

[a] Estimates of the adjusted GMR confidence limits were exponentiated.

[b] Analysis of variance using the natural logarithm of the PK parameter as the response variable; sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect

NOTE: Bioequivalence criteria are met if the 90% CI of the adjusted GMR for $AUC_{0-168,ss}$ and $C_{max,ss}$ are completely within the interval 0.8-1.25.

Source: Table 14.4.6.2

Study P-15086 summary:

Bioequivalence: TDS A (105 cm^2) satisfied the BE criteria (90% CI for the adjusted geometric mean ratio [GMR] within 0.8 to 1.25) for both $AUC_{0-168,ss}$ and $C_{max,ss}$.

TDS B (130 cm^2), met BE criteria for $C_{max,ss}$ but not for $AUC_{0-168,ss}$.

Comments: TDS B (130 cm^2) is not relevant for approval. The proposed for commercialization strengths are the 52.5 cm^2 and 105 cm^2 TDS. [redacted] .

The main efficacy evaluation for Donepezil TDS relies on the effectiveness of Aricept (LD) and is based on a pharmacokinetic (PK) bridging approach. A Request for Routine Biopharmaceutical Inspection was sent to the OSIS requesting clinical and bioanalytical site inspections for BE study P-15086. OSIS determined that inspections are not warranted at this time as these sites were recently inspected (Please refer to Decline to Inspect_NDA 212304, DARRTS 05/07/2020).

P-15086 Sub-Study:

A Phase 1, Randomized, Open-Label, 2-Way Crossover Study to Compare the Relative Bioavailability of Two Corplex Donepezil Transdermal Delivery Systems Manufactured Using Active Pharmaceutical Ingredient from Two Different Suppliers

This P-15086 Sub-Study was an open-label, randomized, 2-period, 2-way crossover design PK study in 47 healthy, white, adult male or female subjects.

Supplier 1 refers to Treatment D (Donepezil TDS D): Target dosage of 5 mg/day donepezil (1 x 50 cm^2 Corplex Donepezil TDS containing API from the original manufacturer [Supplier 1])

Supplier 2 refers to Treatment E (Donepezil TDS E): Target dosage of 5 mg/day donepezil (1 x 50 cm^2 Corplex Donepezil TDS containing API from a new manufacturer [Supplier 2]).

Notes: Suppliers and Lot Numbers: [redacted], C1607109; [redacted], C1610331. Sponsor did not specify which supplier(s) will be used for the TBM formulation.

Subjects received two different once-weekly Corplex Donepezil TDS treatments (Treatments D and E), each administered for 1 week, in two different treatment periods (Treatment Period 1 and Treatment Period 2).

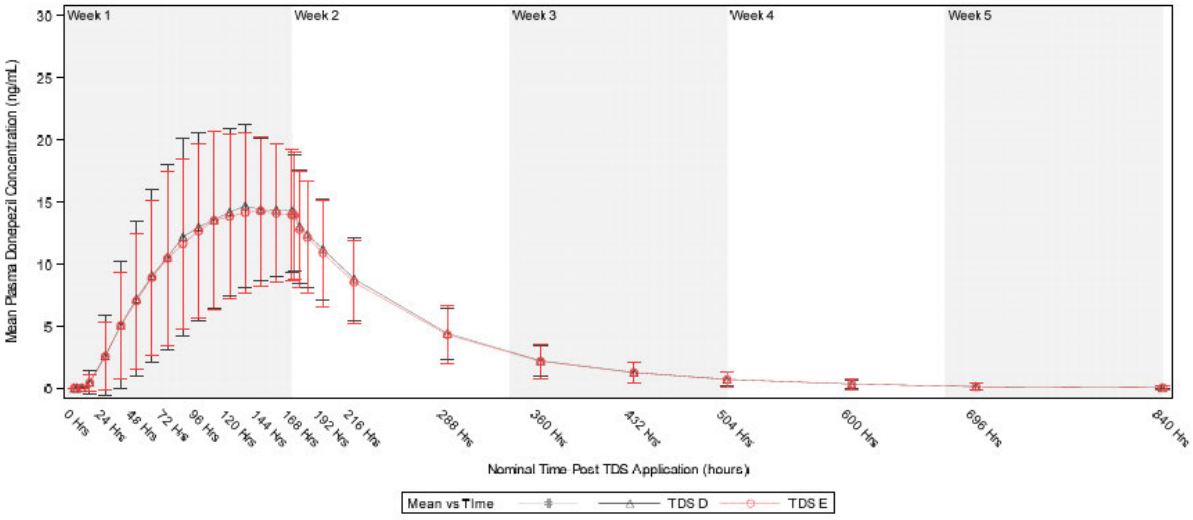
The Corplex Donepezil TDS 5 mg/day (50 cm^2) was placed on the subject's mid-back.

Bioanalytical: Donepezil in human plasma was quantified using a validated HPLC-MS/MS (Method 2; [redacted] CA23945-01). The performance of the method during the analysis of the samples of Study P-15086 and the Sub-Study was adequate. In addition, OSIS determined that inspections of the clinical and bioanalytical sites are not warranted at this time as these sites were recently inspected ([redacted] and [redacted], respectively).

Results:

Supplier 2 was bioequivalent to reference Supplier 1 (90% CI within prespecified 0.8 to 1.25 range) for C_{max}, AUC_{inf}, and AUC_{0-168}.

Mean (± SD) of Plasma Donepezil Concentrations from Days 1 to 36 – Linear Scale (P-15086 Sub-Study



Summary of Mean (%CV) Donepezil Pharmacokinetic Parameters (P-15086 Sub-Study, Pharmacokinetic Set)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-168} (h.ng/mL)	AUC_{inf} (h.ng/mL)	$T_{1/2}$ (hr)
D (n = 44)	16.247 (44.9%)	144.78 (18.3%)	1655.051 (54.9%)	3176.237 (41.7%)	89.81 (28.4%)
E (n = 47)	15.780 (43.4%)	144.48 (21.4%)	1616.784 (52.8%)	3089.919 (44.2%)	81.76 (24.3%)

Abbreviations: API = active pharmaceutical ingredient; AUC_{0-168} = area under the plasma concentration-time curve from Time 0 to 168 hours, AUC during week 1; AUC_{inf} = Area under the concentration-time curve from Time 0 to infinity; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; D = 5 mg/day donepezil (1 x 50 cm^2 Corplex Donepezil TDS containing API from Supplier 1) applied at Hour 0 on Day 1 (Week 1) for a duration of 1 week; E = 5 mg/day donepezil (1 x 50 cm^2 Corplex Donepezil TDS containing API from Supplier 2) applied at Hour 0 on Day 1 (Week 1) for a duration of 1 week; hr = hour; h.ng/mL = the units for AUC arrived at when using the trapezoidal rule to calculate the area under the concentration (ng/mL) versus time (h) curve; n = the number of subjects included in the analysis; TDS = transdermal delivery system; T_{max} = Time to reach maximum observed plasma concentration, $T_{1/2}$ = apparent first-order terminal elimination half-life.

Comments:

Sponsor claims (page 20, Sect 2.7.2.2): The final to-be-marketed formulation was used in 6 Phase 1 studies (Studies P-15086, P-15086 Sub-Study, P-16010, P-16011, P-16012, P-16039) conducted under US IND # (b) (4). However, the manufacturing process for the patch used in the "pivotal" study 15086 is not the same as the proposed manufacturing process for the commercial product.

Study Category	Assessment						
	Study Number	Brief Title	Formulation Stage	Parent PK	Metabolite PK	PD	Summarized in Module 2.7.2
Early Development	P-15007	Prototype Evaluation	Prototype	Yes	Yes	No	Yes
	P-15081	Formulation Selection	Near-Final	Yes	Yes	No	Yes
	P-16007	Adhesion Optimization	Near- Final	Yes	No	No	Yes
Key - Pivotal	**P-15086**	Steady-state Bioequivalence	Final*	Yes	No	**Yes**	Yes
Key - Supportive	**P-16011**	Skin Irritation/ Sensitization	Final	No	No	No	No
	P-16012	Relative Bioavailability - Application Site	Final	Yes	No	No	Yes
	P-16039	Relative Bioavailability – Applied Heat	Final	Yes	No	No	Yes
Supportive	P-16010	Safety/ Tolerability and Adhesion	Final	No	No	No	No
	P-15086 Sub-Study	Relative Bioavailability - API Supplier	Final*	Yes	No	No	Yes

*Indicate (b) (4) from final formulation with no expected impact on product

(b) (4)

per OPQ, this change in the manufacturing process is significant enough that a PK bridge is needed (i.e. the in vitro methods show a change that cannot be sufficiently explained due to several confounding factors). Bioequivalence has been established between Once-Weekly Corplex Donepezil and the LD Aricept® at steady state in study 15086. However, an in vivo bridge is lacking between the product used in 15086 and the commercial product (i.e. the process used for studies 16010, 16012). PK data from these studies, if appropriate, could be the additional in vivo PK bridging study between the products produced from two manufacturing processes.

Currently, the PK bridging results are not adequate due to the following reasons:

1. The commercial sizes of the product are 52.5 cm^2 and 105 cm^2, which were used in study 15086. However, different sizes (53.5 cm^2 and 107 cm^2) were used in 16010 and 16012.
2. Study P-16010 (Steady State Bioequivalence of Once-Weekly Corplex Donepezil 10 mg Transdermal Delivery System Compared to Daily Oral Administration of Aricept®) does not have any PK results, i.e. PK samples were collected but not analyzed. It is not clear whether samples were retained and if so, whether these samples could be analyzed and used for a PK bridge. Study 16010 was completed March 2018. Based on the Summary table (Version: Final 21 AUG 2019 Page 351 of 4631) for Bioanalytical Method 2 used for analysis of plasma samples in Studies P-15086 and 16012, long-term stability for donepezil in plasma has been established up to 177 days at -20°C. Therefore, those retained samples may not be stable to be used for the measurement of donepezil concentrations.

Freeze-Thaw Stability (Cycles)	6 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light
Long-Term Storage Stability (Days)	Long-Term Stability: 177 days in polypropylene tubes at -20°C

3. Study 16012 (Crossover Study to Evaluate the Pharmacokinetics of Corplex Donepezil 10 mg Transdermal Delivery System Applied to Different Body Locations) is a single-dose study and does not include the LD Aricept®. Therefore, the PK comparison need to be cross study comparison (15086 to 16012), which is not optimal.

Summary:
Several additional OPQ issues preclude approval of this NDA in this review cycle, refer to the Discipline Review Letter (DRL). If the OPQ issues are resolved, a PK bridging study is needed between the product used in study 15086 and the commercial product (i.e. the product used for studies 16010, 16012). PK data from these studies, if appropriate, could be used as the additional in vivo bridge between the two manufacturing processes. If the sponsor can't use 16010 or 16012 for the reasons above (cross study, single dose, unstable samples), then the sponsor needs to conduct a new in vivo BE study. The approval of ADLARITY will depend on this additional PK bridging results.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

This question is premature. Refer to Section 3.3.1.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

This question is premature. Refer to Section 3.3.1.

3.3.4 Bioavailability of Corplex Donepezil TDS when Applied to Different Body Locations

Study P-16012 was conducted to compare the relative bioavailability of donepezil after Corplex Donepezil TDS application to different locations on the body (with back as the reference location).

Study P-16012 was an open-label, 3-way crossover single dose PK study conducted in 66 healthy male and female subjects. All subjects received a single application of once-weekly Corplex Donepezil TDS applied to 3 different body locations on each subject (TDS Back, TDS Thigh, and TDS Buttock) during 3 different, consecutive treatment periods (Treatment Periods 1, 2, and 3).

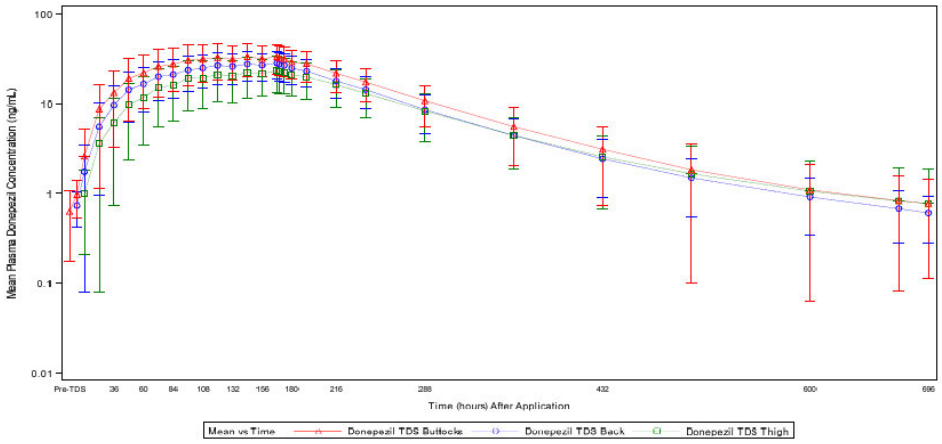
In each treatment period the subjects received a target dose of 10 mg/day Corplex Donepezil TDS (e.g. 107 cm^2) for 1 week, with 5-week washout intervals between the treatment periods.

Sixty subjects entered Treatment Period 2 and 3 and received one dose of Corplex Donepezil TDS according to their randomized application site sequence. A total of 59 subjects completed the study.

Notes: The PK samples were analyzed using a validated LC-MS/MS method (Method 2). The performance of the method during the analysis of the samples of Study P-16012 was adequate. The same method was used for analysis of plasma samples in study P-15086. (Please refer to OSIS Decline to Inspect_NDA 212304, DARRTS 05/07/2020).

.

Study P-16012: Mean (± SD) of Plasma Donepezil Concentrations (ng/mL) from Day 1 to Day 30 by Application Site – Semi-log Scale



Abbreviations: TDS Back = Back application of Corplex Donepezil TDS = 10 mg/day Donepezil (1 × 107 cm^2 Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days, TDS Buttock = Buttock application of Corplex Donepezil TDS = 10 mg/day Donepezil (1 × 107 cm^2 Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days, TDS Thigh = Thigh application of Corplex Donepezil TDS = 10 mg/day Donepezil (1 × 107 cm^2 Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days, TDS = transdermal delivery system, vs = versus.
Source: Figure 14.4.4.2.1

Mean exposure (AUCinf and Cmax) following Corplex Donepezil TDS application to TDS Thigh was 14% to 18% lower than for TDS Back, whereas for TDS Buttock, exposure was 21% to 24% higher than for TDS Back.

Following Corplex Donepezil TDS removal after 168 hours, the elimination phases were similar for all body locations.

Study P-16012: Summary of Donepezil Pharmacokinetic Parameters

Treatment	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-168} (h*ng/mL)	AUC_{inf} (h*ng/mL)	K_{el} (h^{-1})	$T_{1/2}$ (h)	AUC_{0-t} h*ng/mL	%Extrap (%)	t_{lag} (h)
TDS Back (N = 61)	29.58 (35.3)	168.0 (96.0-174)	3094 (41.6)	6215 (36.9)	0.007481 (26.5)	97.52 (20.2)	6136 (37.1)	1.363 60.3	8.001 (50.9)
TDS Thigh (N = 63)	24.33 (44.6)	168.0 (96.0-192)	2387 (54.8)	5358 (50.4)	0.007137 (25.5)	103.3 (27.2)	5229 (49.0)	2.130 112.8	12.14 (59.4)
TDS Buttock (N = 62)	35.91 (38.1)	144.0 (72.0-174)	3894 (48.1)	7723 (44.0)	0.007567 (24.6)	96.91 (24.0)	7619 (43.7)	1.311 64.5	7.806 (65.2)

Source: Table 14.4.2.1

Study P-16012: Statistical Comparison of Primary Pharmacokinetic Endpoints

Treatment	n	Comparison	Adjusted GMR	90% CI
AUC_{0-168} (h*mg/mL)				
TDS Thigh	56/57	TDS Thigh/TDS Back	0.705	(0.638, 0.779)
TDS Buttock	57/57	TDS Buttock/TDS Back	1.234	(1.118, 1.362)
AUC_{inf} (h*mg/mL)				
TDS Thigh	56/57	TDS Thigh/TDS Back	0.806	(0.744, 0.873)
TDS Buttock	57/57	TDS Buttock/TDS Back	1.230	(1.136, 1.331)
C_{max} (ng/mL)				
TDS Thigh	56/57	TDS Thigh/TDS Back	0.779	(0.719, 0.844)
TDS Buttock	57/57	TDS Buttock/TDS Back	1.215	(1.121, 1.316)

Results based on linear model with treatment location as a fixed effect.

Source: Table 14.4.3.1

Study P-16012 Summary:

- Corplex Donepezil TDS (10 mg/day, 107 cm^2) applied to different body locations (back, thigh, and buttocks) was generally well tolerated in healthy subjects.
- Donepezil exposure as assessed by the PK parameters of AUC_{inf} and C_{max} was 21% to 24% greater for the TDS Buttock versus TDS Back application (reference site).
- Donepezil exposure as assessed by the PK parameters of AUC_{inf} and C_{max} was 14% to 18% lower for TDS Thigh versus TDS Back application (reference site).
- Bioequivalence criteria (90% CI 0.8 to 1.25) were not met for C_{max} or AUC (AUC_{0-168} or AUC_{inf}) for either TDS Thigh or TDS Buttock application compared to TDS Back (reference site).
- Per the sponsor, all 3 patch sites (TDS Back, TDS Thigh, and TDS Buttock) demonstrated good adhesion, with mean adherence approximating or greater than 90%.

Comment: In the label, sponsor does not specify the site application: (b) (4) .

Recommendations: Since in the pivotal study P15086 TDS was applied to the back, and the PK in the three patch sites are not BE, Corplex Donepezil TDS should be applied to the back only.

3.3.5 Are there clinically relevant extrinsic factors and what is the appropriate management strategy?

Study P-16039 was conducted to evaluate the effect of heat application on the PK of Corplex Donepezil 5 mg (e.g. 53.5 cm^2) TDS in healthy subjects

Design: randomized, open-label, 2-way crossover study (Main Study) with a voluntary Study Extension Period (Extension Period). A total of 24 healthy, Caucasian, male and female volunteers ≥ 30 years of age (with 10 subjects ≥ 60 years of age) were enrolled in the study.

Twenty-two out of 24 subjects received both treatments in the study; two subjects terminated early. All subjects received a single, 7-day application of TDS (target dose 5 mg/day donepezil) to a naïve location on the back during 2 different, consecutive treatment periods.

Subjects were randomized to one of 2 treatment sequences in each period:

Sequence A: Corplex Donepezil TDS with Applied Heat [Treatment Period 1]/Corplex Donepezil TDS with No Applied Heat [Treatment Period 2]

Sequence B: Corplex Donepezil TDS with No Applied Heat (no application of heat during the 7-day TDS wear) [Treatment Period 1]/Corplex Donepezil TDS with Applied Heat [Treatment Period 2])

Heat Periods: Set of three 7-hour Heat Intervals (consists of Heat Sessions and Rest Periods) occurring on Days 2, 4, and 7 of the once-weekly TDS. The three Heat Intervals consisted of three 2-hour heat sessions at 42°± 2°C (107.5 ± 3.5°F) and Rest Periods. Per the sponsor, this heat exposure approximates overnight use of a heating pad 3 days a week.

Primary PK variables for donepezil: $AUC_{0\text{-}168}$, AUC_{inf}, C_{max}

Secondary PK variables for donepezil:

$AUC_{24\text{-}32}$ corresponding to the first of three Heat Intervals

$AUC_{72\text{-}80}$ corresponding to the second of three Heat Intervals

$AUC_{144\text{-}152}$ corresponding to the third of three Heat Intervals

Notes: The PK samples were analyzed using a validated LC-MS/MS method (Method 2). The performance of the method during the analysis of the samples of Study P-16039 was adequate. The same method was used for analysis of plasma samples in study P-15086.

Study P-16039: Summary of Mean (CV%) Pharmacokinetic Parameters for Donepezil

Treatment	C_{max} (ng/mL)	T_{max} (h)	AUC_{24-32} (h*ng/mL)	AUC_{72-80} (h*ng/mL)	$AUC_{144-152}$ (h*ng/mL)	AUC_{0-168} (h*ng/mL)	AUC_{inf} (h*ng/mL)	K_{el} (h-1)	$T_{1/2}$ (h)
Corplex Donepezil TDS + Applied Heat (n = 20)	15.2690 (43.6%)	139.917 (19.1)	34.69 (86.9%)	85.45 (56.5%)	104.46 (41.0%)	1506.10 (47.5%)	3069.66 (40.3)	0.007887 (37.4%)	99.872 (36.5%)
Corplex Donepezil TDS + No Applied Heat (n = 21)	14.1906 (44.0%)	140.821 (18.5)	23.32[a] (77.6%)	71.01[b] (51.0%)	96.82 (46.1%)	1429.70 (46.6%)	3060.70 (50.6%)	0.007950 (34.8%)	99.020 (38.5%)

Abbreviations: AUC= area under the plasma concentration-time curve, AUC_{24-32} = AUC from 24 to 32 hours, corresponding to the first of three Heat Intervals, AUC_{72-80} = AUC from 72 to 80 hours, corresponding to the second of three Heat Intervals, $AUC_{144-152}$= AUC from 144 to 152 hours , corresponding to the third of three Heat Intervals, AUC_{0-168} = AUC from Time 0 to 168 hours, AUC_{inf} = AUC from Time 0 to infinity, BLQ = below the limit of quantification, Corplex Donepezil TDS + Applied Heat = 5 mg per day donepezil (1 x 53.5 cm^2 Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) + heating pad for three 2-hour Heat Sessions over a single 7-hour Heat Interval on Days 2, 4, and 7, Corplex Donepezil TDS + No Applied Heat = 5 mg per day donepezil (1 x 53.5 cm^2 Corplex Donepezil TDS) applied at Hour 0 on Day 1 + No heating pad, C_{max} = maximum observed concentration, CV = coefficient of variation, K_{el} = apparent first-order terminal elimination rate constant, n = the number of nonmissing observations, PK = pharmacokinetic, SAP = Statistical Analysis Plan, $T_{1/2}$ = apparent first-order terminal elimination half-life, TDS = transdermal delivery system, T_{max} = time to reach maximum observed concentration.

Note: The limit of quantification for the assay is 0.300 ng/mL. All concentration values which are BLQ are treated as per Section 9.3.1 of the SAP in the calculation of PK parameters. Missing and zero values for PK parameters were not included in the calculation of geometric mean and geometric mean CV%. Subject (b) (6) had an early TDS removal in Treatment Period 1 (Corplex Donepezil TDS without applied heat). The AUC_{24-32} was the only parameter included from Treatment Period 1 for this subject. Subject (b) (6) had an early TDS removal in Treatment Period 1 (Corplex Donepezil TDS without applied heat). The AUC_{24-32} and AUC_{72-80} were the only parameters included from Treatment Period 1 for this subject. All calculated parameters in Treatment Period 1 (TDS + Applied Heat) for subject (b) (6) were excluded due to incomplete Heat Sessions. All calculated parameters in Treatment Period 1 (TDS + Applied Heat) for subject (b) (6) were excluded due to incomplete Heat Sessions.

a. The total number of observed values (n) = 23.

b. The total number of observed values (n) = 22.

Source: Table 14.4.2.1.

Relative Bioavailability Analysis of Plasma Pharmacokinetic Parameters (for TDS + Applied Heat/TDS + No Applied Heat)

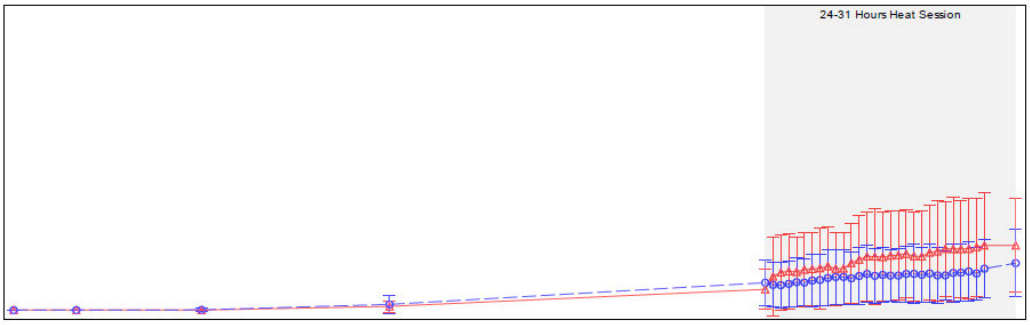
Treatment	n	Adjusted Geometric Mean[a]	Comparison	Adjusted GMR	P-value	90% Confidence Interval
AUC_{0-168} (h*ng/mL)						
Corplex Donepezil TDS + Applied Heat	20	1365.88	Corplex Donepezil TDS + Applied Heat/ Corplex Donepezil TDS + No Applied Heat	1.107	0.1301	(0.990, 1.238)
Corplex Donepezil TDS + No Applied Heat	19	1233.33				
C_{max} (ng/mL)						
Corplex Donepezil TDS + Applied Heat	20	14.0866	Corplex Donepezil TDS + Applied Heat/ Corplex Donepezil TDS + No Applied Heat	1.129	0.0613	(1.016, 1.254)
Corplex Donepezil TDS + No Applied Heat	19	12.4782				
AUC_{24-32} (h*ng/mL)						
Corplex Donepezil TDS + Applied Heat	20	27.21	Corplex Donepezil TDS + Applied/ Corplex Donepezil TDS + No Applied Heat	1.600	0.0020	(1.276, 2.006)
Corplex Donepezil TDS+ No Applied Heat	20	17.01				
AUC_{72-80} (h*ng/mL)						
Corplex Donepezil TDS + Applied Heat	20	75.16	Corplex Donepezil TDS + Applied Heat/ Corplex Donepezil TDS + No Applied Heat	1.227	0.0191	(1.069, 1.409)
Corplex Donepezil TDS + No Applied Heat	20	61.25				
$AUC_{144-152}$ (h*ng/mL)						
Corplex Donepezil TDS + Heat	20	97.53	Corplex Donepezil TDS + Heat/ Corplex Donepezil TDS + No Applied Heat	1.150	0.0261	(1.041, 1.271)
Corplex Donepezil TDS + No Applied Heat	19	84.81				

Source: Table 14.4.3.1

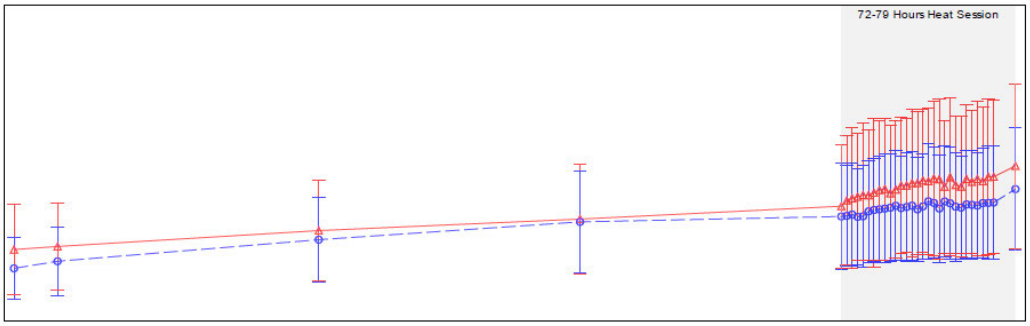
The primary PK parameters were not significantly different between heated and non-heated conditions: AUC_{0-168} (P-value: 0.1301), AUC_{inf} (P-value: 0.2508), and C_{max} (P-value: 0.0613). However, mean plasma donepezil concentration profiles showed transitory increases during Heat Sessions for heated compared with control conditions.

Relative bioavailability of Corplex Donepezil TDS with applied heat versus no heat was 1.600, 1.227 and 1.150 for AUC_{24-32}, AUC_{72-80} and $AUC_{144-152}$, respectively.

Mean (± SD) Plasma Donepezil Concentration versus Time from Hours 0 to 32



Mean (± SD) Plasma Donepezil Concentration versus Time from Hours 34 to 80



Source: Figure 14.4.6.1.1.

Comments: The significance of these increases (up to 60% increase in AUC_{24-32}) was discussed with the clinical team. The product should have heat exposure limitations. Indeed, the Prescribing Information (Section 2.4 and Section 17) states to avoid long exposure to external heat sources (e.g., excessive sunlight, saunas, solariums or heating pads).

Recommendation: "Avoid applying heat" or a similar statement should be added to the labeling.

4. APPENDICES

4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Concentrations of donepezil in human plasma was measured by validated bioanalytical methods. Two liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) methods were developed and validated.

A validated LC/MS/MS method (**Method 1**, (b) (4)-BM15339) for the quantitation of donepezil and its active metabolite 6-O-desmethyl donepezil in human plasma was used in three studies (P-15007, P-15081, and P-16007). The metabolite 6-O-desmethyl donepezil was measured in 2 of these studies (P-15007 and P-15081). The method was validated for quantitation of donepezil and 6-O-desmethyl donepezil in human plasma over the concentration ranges of 0.209 ng/mL to 41.799 ng/mL and 40.628 pg/mL to 8125.624 pg/mL, respectively (Validation Report # (b) (4)-VR15339). The validation of Method 1 was performed by (b) (4) and was approved 14 May 2015. Addendum 03 (dated 05 December 2015) changed the calibration curve range of 6-O-desmethyl donepezil to 10.000 - 2000.000 pg/mL when it was observed during study P-15007 that a lower calibration range for the metabolite was needed.

Comments: Since, per the Aricept label, donepezil has a major active metabolite (6-O-desmethyl donepezil, M1), the PK bridge between the oral and transdermal products should be based on bioequivalence (BE) of both parent drug and metabolite. However, at the preIND meeting sponsor argued that, based on Study P15007 data, M1: Parent ratio of < 1% after both transdermal and oral administration, therefore BE should be based on parent drug only.

However, several issues were identified with the bioanalytical method (Method 1) validation and performance of the method during the analysis in Studies P-15007 and P-15081, see Information Requests below. These issues needed to be resolved in order to determine whether BE needs to be based on both parent and metabolite or on parent only.

Information Request (Feb 18, 2020):

Please refer to the Validation Report # (b) (4)-VR15339 of Method 1 performed by (b) (4) for the determination of donepezil and its metabolite 6-O-desmethyl donepezil in human plasma used in studies P-15007, P-15081, and P-16007.

Per the Bioanalytical Method Validation Guidance (2018), “During method development, the sponsor should determine the chemical stability of the analyte in a given matrix, including the effects of sample collection, handling, and storage of the analyte”.

We note that Long Term Stability of Donepezil and its metabolite 6-ODesmethyl Donepezil in human plasma stored in freezer at -20°C for 111 days has been established, however, it is not

clear whether Method 1 validation included assessments for Freeze-Thaw Stability for parent and metabolite, Stability of Analyte During Sample Collection and Handling, etc.

Per Khuroo et al, labile metabolites of donepezil are prone to being converted to the parent compound, which could complicate estimating drug and active metabolite concentrations in human plasma. You should provide similar validation summary as the one provided for Method 2, (b) (4) Study ZZ49214-01.

We also refer to Addendum 03 (dated 05 December 2015) of Method 1. The metabolite 6-O-desmethyl donepezil calibration curve range had been changed "when it was observed during study P-15007 that the original calibration range was not sufficient". Please clarify how the samples for which original calibration range was not sufficient were treated.

In addition, we found numerous discrepancies in reporting the results, for example:

In Protocol P-15081:

4 BIOANALYSIS

Validated methods were used to determine the concentration of donepezil and 6-O-desmethyl donepezil in the plasma samples collected. The lower limit of quantification was 0.207 ng/mL for donepezil and 10.222 pg/mL for the metabolite. The details of this analysis are described in a separate report from the bioanalytical laboratory.

However, in 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods:

Table 6 Donepezil Assay Method 1 - Lower and Upper Limits of Quantitation

	LLOQ	ULOQ
Donepezil	0.209 ng/mL	41.799 ng/mL
6-O-Desmethyl Donepezil		
Original range	40.628 pg/mL	8125.624 pg/mL
Revised range[a]	10.000 pg/mL	2000.000 pg/mL

Abbreviations: LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation

In Protocol: P-15007:

6-O-Desmethyl Donepezil PK Parameters for Group 1 & 2 concentrations are reported as pg/ml, however for Group 3 they are reported as ng/ml, see below.

Treatment	Statistic	t_{hr} (h)	C_{max} (pg/mL)	C_{max,D^*} (pg/mL)	AUC_{D^*} (h*pg/mL)
A: Donepezil TDS 3 x LF 50cm²	Mean (SD)	48.167 (64.772)	46.4068 (20.8173)	32.2722 (24.6872)	654.0 (494.0)
	Min, Max	12.00, 180.00	19.350, 83.330	0.000, 73.390	0, 1460
	Median	24.00	44.9405	26.7575	538.7
B: Donepezil TDS 2 x HF 50cm²	Mean (SD)	59.338 (49.982)	37.5623 (14.4326)	31.9760 (15.6487)	563.4 (320.0)
	Min	12.00, 151.98	23.060, 58.320	12.764, 49.630	103, 924
	Median	48.00	34.68	33.1495	546.7
C: Aricept 10 mg	Mean (SD)	0.167 (0.408)	81.8617 (48.0829)	65.3350 (35.4702)*	901.3 (362.8)*
	Min, Max	0.00, 1.00	28.850	29.698, 100.636	509, 1224
	Median	0.00	81.0300	65.6710	971.6

*Calculated on n=3

Parameter (unit)	Mean		Standard Deviation	
	B1	C1	B1	C1
t_{lag} (h)	63.289	3.647	24.640	6.827
$AUC_{D?}$ (h.ng/mL)	621.5	606.4	364.3	294.6
$C_{max,D?}$ (ng/mL)	32.5567	41.8718	21.2544	22.4604
$C_{avg,D?}$ (ng/mL)	25.6783	25.2665	17.0547	12.2754
$t_{max,D?}$ (h)	153.433	-	9.642	-
AUC_{0-24} (h.ng/mL)	-	301.4	-	117.5

You need to correct these discrepancies and send us the revised corresponding study results.

Sponsor Response

The sponsor clarified that Method 1 validation included assessments for freeze thaw stability for 4 cycles, bench-top stability for 6 hours at room temperature, auto-sampler stability for 153 hours at 4ºC and long-term plasma stability for 111 days at -20 ºC, for both the parent drug, donepezil, and its metabolite, 6-O-desmethyl donepezil. All the stability experiments met the acceptance criteria.

In addition, the blood and plasma samples at the clinical site were stored at ice water temperature until transfer to the freezer. According to Khuroo et al, this treatment is sufficient to prevent interconversion of analytes in the samples.

PK sample collection instructions

Req Form	Collection tube	Mix by inversion	Allow to stand for	Centrifuge	Transfer plasma	Further processing	Storage temp.	Shipping instructions
	 EDTA 5 mL (PK)*	8-10 times	place sample immediately in ice-water bath	Centrifuge **within 30 minutes** of collection for 10 minutes at 4°C at 1500 g		 Transfer 1.5 mL into a yellow cap transfer vial 2 mL (primary) and  transfer the remaining volume into a blue cap transfer vial 2 mL (back-up)	-20°C (-4°F)	Frozen Dry Ice shipments Samples will not be shipped via (b) (4) Corium International will schedule the shipments to (b) (4) themselves.

Additional Information

*The time from sample collection to placement in the freezer should not exceed 120 minutes.

All samples were kept in the auto sampler at 4°C during the sample analysis. To confirm autosampler stability of processed samples, the data generated with the stored processed samples in the autosampler were compared to that generated using freshly prepared calibrators.

The sponsor also provided clarification for how the samples for which the original calibration range was not sufficient were treated: The samples were refrozen and stored at -20°C for approximately 90 days, then thawed and re-analyzed for 6-O-desmethyl donepezil using the revised calibration range. Therefore, the samples underwent two freeze thaw cycles, which was within the validated number of acceptable freeze-thaw cycles (4 cycles per the Validation Summary for Method 1, see table below).

Validation Summary for Method 1 (Report (b) (4) -VR15339)

Additional Information	Data
Biological matrix	Human Plasma
Anticoagulant	K_3 EDTA
Detector	AB SCIEX API 5000, 5500 and 6500
Assay Volume Required	200 µL
Regression Type	Weighted Linear (1/concentration^2)
Quantitation Method	Peak area ratio
Over-the-counter Concomitant Testing	Acetaminophen (2.5 µg/mL) Ibuprofen (2.5 µg/mL) Caffeine (2.5 µg/mL) Chlorpheniramine Maleate (2.5 µg/mL) Naproxen (2.5 µg/mL) R, R (-)-Pseudoephedrine) (2.5 µg/mL) Ondansetron Hydrochloride (140.000 ng/mL)

Additional Information	Data			
Quality Control Samples	Donepezil		6-O-Desmethyl Donepezil	
Inter Batch	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)
LLOQ	1.5	96.7	9.1	94.8
Low	2.9	93.0	1.5	94.1
Medium	4.0	96.0	5.0	99.9
High	4.4	95.7	5.0	100.0
Quality Control Samples	Donepezil		6-O-Desmethyl Donepezil	
Intra Batch 1	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)
LLOQ	3.0	96.7	9.4	96.5
Low	2.2	92.8	2.0	92.6
Medium	1.9	97.0	1.7	101.2
High	1.0	96.7	1.5	101.9
Quality Control Samples	Donepezil		6-O-Desmethyl Donepezil	
Intra Batch 2	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)
LLOQ	2.0	95.2	7.9	102.4
Low	1.5	90.5	1.6	94.3
Medium	2.4	91.7	2.7	94.3
High	0.7	91.1	0.7	94.4
Quality Control Samples	Donepezil		6-O-Desmethyl Donepezil	
Intra Batch 3	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)
LLOQ	0.5	98.1	11.9	85.5
Low	1.2	95.7	3.8	95.3
Medium	2.2	99.2	2.8	104.1
High	1.3	99.3	1.1	103.8

Matrix Effect	No significant matrix effect was observed in any of the six human plasma lots that were fortified with donepezil and its metabolite 6-O-Desmethyl Donepezil at the concentration of the low QCs (0.598 ng/mL) and (118.759 pg/mL), samples respectively. No significant matrix effect was observed in any of the six human plasma lots that were fortified with donepezil and its metabolite 6-O-Desmethyl Donepezil at the concentration of the high QCs (31.500 ng/mL) and (6250.480 pg/mL), samples respectively.

Long Term Stability for Stock Solutions (Stock & Substock)	41 days at approximately 300.000 µg/mL for donepezil and 50.000 µg/mL for 6-O-Desmethyl Donepezil in a methanol at 2-8°C
Long Term Stability for Stock Solutions (Internal Standard)	Refer to long-term stability for stock solutions data collected from unlabeled donepezil and its metabolite 6-O-Desmethyl Donepezil for labelled internal standard stability.
Short Term Stability for Stock Solutions (stock)	18 hours at approximately 300.000 µg/mL for donepezil and 50.000 µg/mL for 6-O-Desmethyl Donepezil in a methanol at room temperature under regular light
Short Term Stability for Stock Solutions (Substock)	18 hours at approximately 1671.969 ng/mL for donepezil and 325.025 ng/mL for 6-O-Desmethyl Donepezil in a methanol at room temperature under regular light
Stability of Analyte during Sample Collection and Handling	Up to 180 minutes in human whole blood at room temperature under regular light for donepezil and its metabolite 6-O-Desmethyl Donepezil
Stability of Analyte during Long-Term Stability (Frozen)	Donepezil and its metabolite 6-O-Desmethyl Donepezil in human plasma samples (anticoagulant: K_3EDTA) are stable for 111 days in freezer at -20°C.
Stability of Analyte during Freeze-Thaw Stability	Demonstrated for 4 freeze & thaw cycles at -20°C in LQC & HQC level under regular light for donepezil and its metabolite 6-O-Desmethyl Donepezil
Stability of Analyte during Short-Term Stability (Room Temp)	Samples were stable for 6 hours at LQC & HQC level on bench at room temperature under regular light for donepezil and its metabolite 6-O-Desmethyl Donepezil
Batch Size	217 injections

*Data Source: Validation Report (b) (4) VR15339 and all Addenda

In addition, sponsor replaced the prior versions of Clinical Study Reports (CSRs) P-15007 and P-15081 with Amended Versions to address the discrepancies in the CSRs and PK Reports. For example:

Description of and Rationale for Change
Reference to Figure 12 added to the text preceding this figure; corrected the source figure number. Rationale for change: Typographical error/transcription error.
The units in the column headers of 4 tables had a typographical error, where the units were incorrectly stated as "ng/mL" instead of "pg/mL"; these have been corrected to state "pg/mL" in the following tables: Table 14.4.2.1.3: units in 4 column headers changed from ng/mL to pg/mL Table 14.4.2.1.4: units in 4 column headers changed from ng/mL to pg/mL Table 14.4.2.2.3: units in 5 column headers changed from ng/mL to pg/mL Table 14.4.2.2.4: units in 4 column headers changed from ng/mL to pg/mL
The units in the column headers for 4 listings had a typographical error, where the units were incorrectly stated as "ng/mL" instead of "pg/mL"; these have been corrected to state "pg/mL" in the following listings: Listing 16.2.10.2.1.3.1: units in 4 column headers changed from ng/mL to pg/mL Listing 16.2.10.2.1.3.2: units in 4 column headers changed from ng/mL to pg/mL Listing 16.2.10.2.2.3.1: units in 5 column headers changed from ng/mL to pg/mL Listing 16.2.10.2.2.3.2: units in 4 column headers changed from ng/mL to pg/mL Rationale for change: Typographical error.

Comments:

- The sponsor's response to the IR to clarify the issues and correct the discrepancies is acceptable.
- Method 1 bioanalytical issues have been addressed adequately by the sponsor.

Method 2

A validated LC/MS/MS method (Method 2, BAM SOP ZZ49214-01) was used for the quantitation of donepezil in human plasma in Studies P-15086, P-15086 Sub-Study, P-16012, and P-16039. Method 2 was validated by (b) (4) over the concentration range of 0.300 ng/mL to 45.0 ng/mL.

A summary of the Method 2 validation results is provided below.

Information Requested	Data
Validation Summary	(b) (4) Validation Study ZZ49214-01
Analyte	Donepezil
Internal Standard (IS)	d_4-Donepezil
Method Description	Liquid-liquid extraction with analysis/detection by LC-MS/MS
Limit of Quantitation (ng/mL)	0.300 ng/mL
Average Recovery of Drug (% Mean)	85% at 0.900 ng/mL 89% at 3.50 ng/mL 82% at 35.0 ng/mL
Average Recovery of IS (% Mean)	83%
Standard Curve Concentrations (ng/mL)	0.300, 0.600, 1.50, 5.00, 10.0, 20.0, 37.0, and 45.0 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 0.900, 3.50, and 35.0 ng/mL
QC Intra-Batch Precision Range (% CV)	2.1 to 5.9%
QC Intra-Batch Accuracy Range (% Bias)	-11.3 to 10.3%
QC Inter-Batch Precision Range (% CV)	2.7 to 9.8%
QC Inter-Batch Accuracy Range (% Bias)	-3.0 to 5.4%
Bench-Top Stability (Hrs)	Short-Term Stability: 27 hours in polypropylene tubes at ambient temperature under white light Cumulative Short-Term Stability: 54 hours in polypropylene tubes at ambient temperature under white light (total of all thaw cycles)
Stock Stability (Days)	Long-Term Stability for Stock Solutions (Stock): 365 days at approximately 1000 µg/mL in methanol in a polypropylene container at -20°C
Processed Stability (Hrs)	Post-Preparative Stability: 177 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 81 hours in a polypropylene 96 well plate at 5°C
Freeze-Thaw Stability (Cycles)	6 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light
Long-Term Storage Stability (Days)	Long-Term Stability: 177 days in polypropylene tubes at -20°C
Dilution Integrity	Up to 200 ng/mL, diluted 20-fold
Selectivity	No significant interference at the retention time and mass transition of donepezil was observed from endogenous components in any of the 10 human plasma (EDTA) lots screened or of d_4-donepezil (IS) in any of the 10 human plasma (EDTA) lots screened

Additional Information			
Matrix		Human Plasma	
Anticoagulant		K_2EDTA	
Bioanalytical Method (BAM) SOP Number		BAM SOP ZZ49214-01	
Detector		AB SCIEX API 4000™	
Assay Volume Required		0.0500 mL	
Regression Type		Weighted linear (1/concentration^2)	
Quantitation Method		Peak area ratio	
Over-the-Counter Cocktail Testing		Acetaminophen (25.0 µg/mL) Atorvastatin (100 ng/mL) Caffeine (20.0 µg/mL) Cetirizine (500 ng/mL) Dextromethorphan (25.0 ng/mL) Ethinyl Estradiol (0.500 ng/mL) Famotidine (200 ng/mL) Ibuprofen (20.0 µg/mL) Levonorgestrel (5.00 ng/mL) Metformin (2.00 µg/mL) Omeprazole (300 ng/mL) Ondansetron (200 ng/mL) Pseudoephedrine (500 ng/mL) Salicylic Acid (100 µg/mL)	
Selectivity from Metabolites Not Quantified by the Method		6-O-Desmethyl Donepezil (10.0 ng/mL) Desbenzyl Donepezil (10.0 ng/mL) 5-O-Desmethyl Donepezil (10.0 ng/mL)	
Quality Control Samples		Precision (% CV)	Accuracy (% Bias)
Inter-Batch	**LLOQ**	9.8	-3.0
	Low	7.2	0.4
	Medium	4.4	5.4
	High	2.7	-1.1
Intra-Batch (Batch 12) **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	5.9	-6.7
	Low	2.9	-2.3
	Medium	2.8	3.7
	High	2.4	-0.3
Intra-Batch (Batch 13) **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	3.7	-11.3
	Low	3.8	-5.7
	Medium	3.1	2.3
	High	2.1	-3.1
Intra-Batch (Batch 17) **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	2.6	8.7
	Low	2.8	9.3
	Medium	3.0	10.3
	High	2.6	-0.3
Matrix Effect		No significant matrix effect was observed in any of the 10 human plasma (EDTA) lots that were fortified with donepezil at the concentration of the LLOQ (0.300 ng/mL) or in any of the 10 human plasma (EDTA) lots that were fortified with donepezil at the concentration of the high QC (35.0 ng/mL) samples	
Hemolyzed Sample Integrity		No significant interference for donepezil was observed in any of the 3 hemolyzed human plasma (EDTA) lots (fortified with 5% whole blood) that were fortified at the concentration of the LLOQ (0.300 ng/mL) or in 2 of the 3 hemolyzed human plasma (EDTA) lots (fortified with 5% whole blood) that were fortified at the concentration of the high QC (35.0 ng/mL) samples	

Sample Shipping Stability	5 days in polypropylene tubes at -80°C
Long-Term Stability for Stock Solutions (Substock)	230 days at 1000 ng/mL in methanol in a polypropylene container at -20°C
Long-Term Stability for Stock Solutions (Internal Standard)	Refer to long-term stability for stock solutions data collected from unlabeled donepezil for labeled internal standard stability
Short-Term Stability for Stock Solutions (Stock)	22 hours at approximately 1000 µg/mL in methanol in a polypropylene container at ambient temperature under white light
Short-Term Stability for Stock Solutions (Substock)	22 hours at 1000 ng/mL in methanol in a polypropylene container at ambient temperature under white light
Short-Term Stability for Stock Solutions (Internal Standard Stock)	Refer to short-term stability for stock solutions data collected from unlabeled donepezil for labeled internal standard stability
Short-Term Stability for Stock Solutions (Internal Standard Substock)	20 hours at 50.0 ng/mL in methanol in a polypropylene container at ambient temperature under white light
Stability of Analyte During Sample Collection and Handling[1]	Up to 120 minutes in human whole blood (EDTA) in polypropylene tubes at ambient temperature under white light
Sample Aliquot Frozen Storage Stability	Samples aliquoted manually at a volume of 0.0500 mL, stored for 120 hours in a polypropylene 96 well plate at -20°C prior to extraction
Known Metabolite Long-Term Stability (Frozen)	Against 6-O-desmethyl donepezil, desbenzyl donepezil, and 5-O-desmethyl donepezil: 48 days in polypropylene tubes at -20°C
Known Metabolite Freeze-Thaw Stability	Against 6-O-desmethyl donepezil, desbenzyl donepezil, and 5-O-desmethyl donepezil: 6 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light
Known Metabolite Short-Term Stability	Co-administered Compound Short-Term Stability Against 6-O-desmethyl donepezil, desbenzyl donepezil, and 5-O-desmethyl donepezil: 27 hours in polypropylene tubes at ambient temperature under white light Co-administered Compound Cumulative Short-Term Stability Against 6-O-desmethyl donepezil, desbenzyl donepezil, and 5-O-desmethyl donepezil: 54 hours in polypropylene tubes at ambient temperature under white light (total of all thaw cycles)
Batch Size	192 injections

Comments:

The Method 2 validation is acceptable.

In addition, a Request for Routine Biopharmaceutical Inspection of the pivotal bioequivalence (BE) study P-15086, including the bioanalytical Method 2 used to analyze the PK samples in the study, has been submitted. OSIS determined that inspections of the bioanalytical site ((b) (4)) is not warranted at this time as the site was recently inspected ((b) (4) , respectively) and no issues were identified during the inspection.

4.2 Pharmacometrics Review

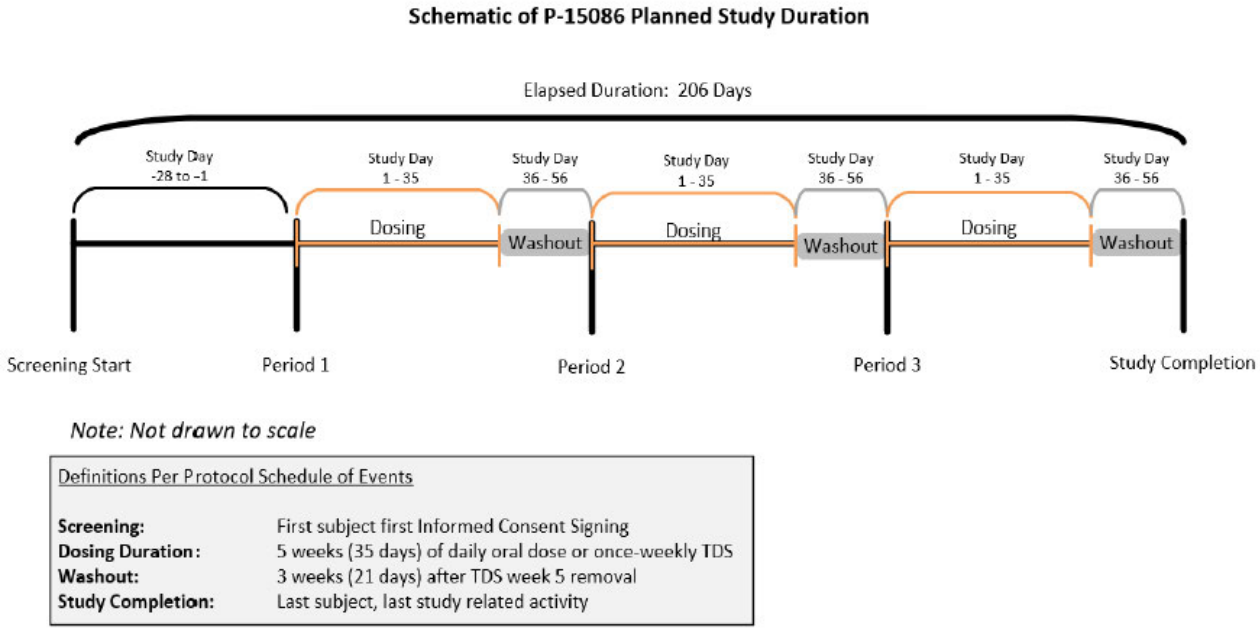
4.2.1 Executive Summary

Corium Inc is seeking an approval for ADLARITY (donepezil transdermal system [TDS]) for the treatment of dementia in patients with mild, moderate and severe Alzheimer's disease. The recommended starting dosage of ADLARITY is one 5 mg/day patch applied to the skin once per week and the maximum recommended dosage of ADLARITY is one 10 mg/day patch applied to the skin once per week. This document is a review of the sponsor's analysis for dose proportionality and switching strategy (from oral donepezil to ADLARITY patch) which supports labeling statements.

4.2.2 Overview of Clinical Study P-15086

The pharmacokinetic (PK) data from the clinical study P-15086 was used to assess both dose proportionality and switching strategy for ADLARITY patch. Briefly, P-150086 was a phase 1, randomized, open-label, 3-way crossover PK study to evaluate the steady-state PK of a once-weekly ADLARITY patch (target dose 10 mg/day donepezil) compared to daily oral ARICEPT® in 60 healthy adult subjects.

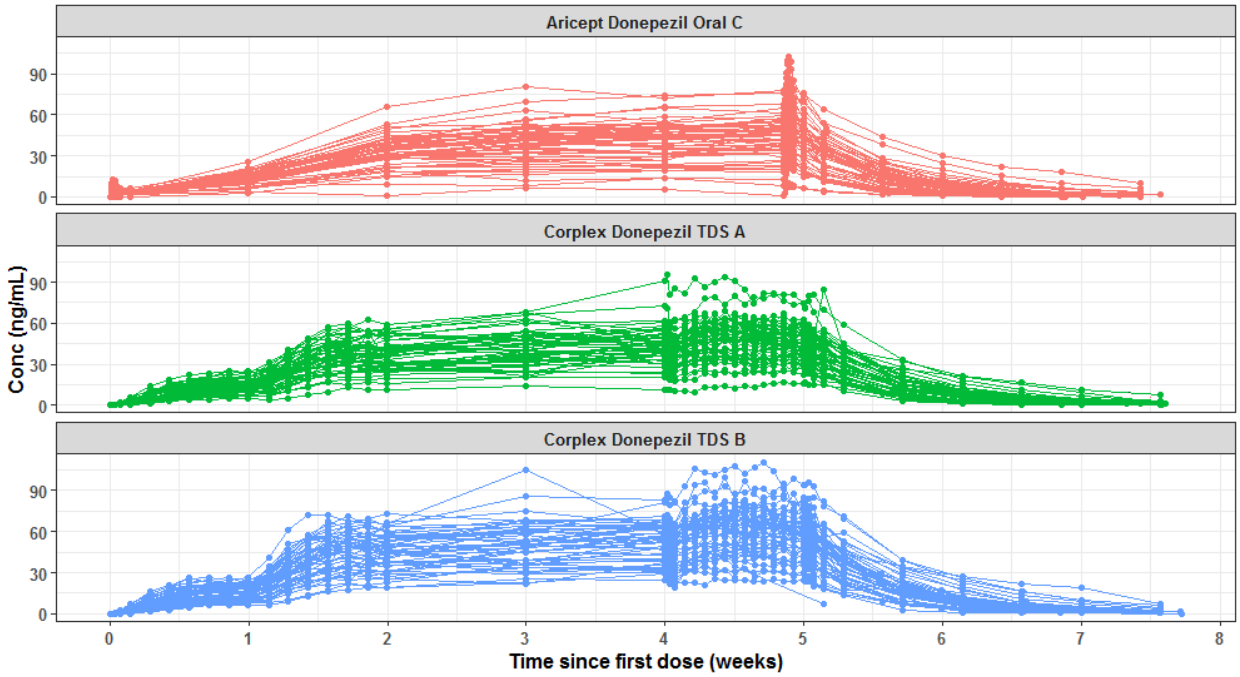
Figure 4-1: Schematics of P-15086 study duration



Source: Corium clinical study report P-15086: Figure 2, Page 32

In the study, subjects were screened and randomized to receive any 1 of 6 treatment sequences (ABC, CAB, BCA, BAC, CBA and ACB), where *treatment A* was a target dose of 5 mg/day donepezil (ADLARITY TDS 50 cm^2 once-weekly) for 1 week followed by doses of 10 mg/day donepezil (ADLARITY TDS A 105 cm^2 once-weekly) for four weeks; *treatment B* was a target dose of 5 mg/day donepezil (ADLARITY TDS 50 cm^2 once-weekly) for 1 week followed by doses of 10 mg/day donepezil (ADLARITY TDS B 130 cm^2 once-weekly); and *treatment C* was a target dose of 5 mg ARICEPT once-daily for 1 week followed by doses of 10 mg ARICEPT once-daily for 4 weeks. All treatments were followed by 3 weeks of washout period (**Figure 4-1**). The resulting individual PK profiles from the three treatments are shown in **Figure 4-2** which shows rich PK sampling during initial (week-1 and 2) and steady-state (week-5) phase for ADLARITY treatment.

Figure 4-2: Individual PK profiles of treatment A (1st week of ADLARITY TDS 50 cm^2 once-weekly followed by 4 weeks of ADLARITY TDS A once-weekly), treatment B (1st week of ADLARITY TDS 50 cm^2 once-weekly followed by 4 weeks of ADLARITY TDS B once-weekly) and treatment C (1st week of oral ARICEPT 5 mg once-daily followed by 4 weeks of oral ARICEPT 10 mg once-daily).

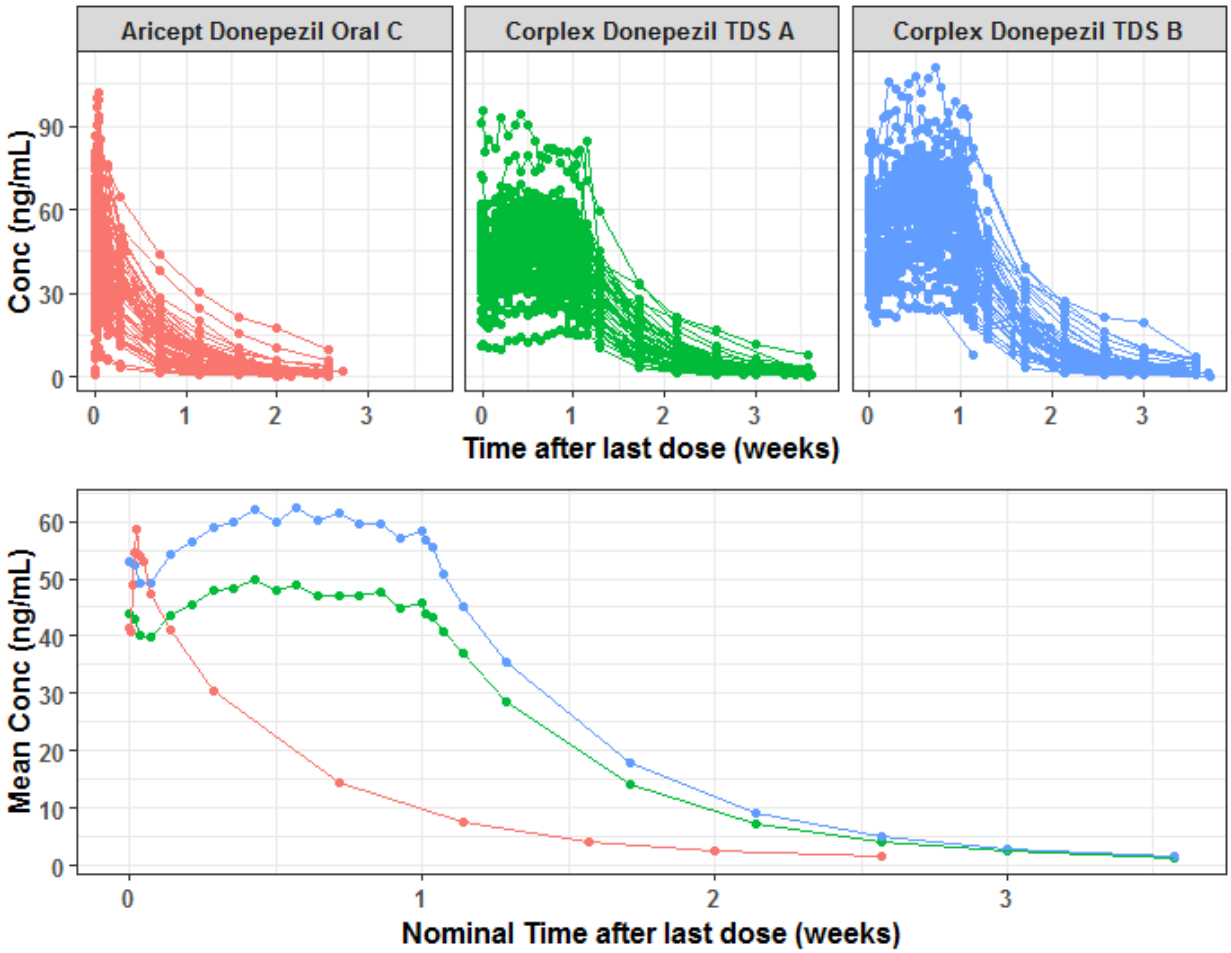


Source: M:\Donepezil_NDA212304_VS\Reviewer\Rscripts\pk_analysis_donepezil.R

The PK data from 5th week of the treatments was used to compare the steady-state PK of once-weekly ADLARITY patch (TDS A and TDS B with a target dose of 10 mg/day donepezil) with once-daily oral ARICEPT (**Figure 4-3**). Sponsor analysis has shown that TDS A met

bioequivalence (BE) criteria for the reference drug i.e. oral ARICEPT 10 mg. The reviewer was able to run the sponsor's analysis and obtained similar results as reported in **Table 4-1**.

Figure 4-3: Top row: Individual PK profiles of donepezil during 5th week by type of formulations; Bottom row: Median PK profiles of donepezil during 5th week by formulation type. Red color indicates oral donepezil, green color indicates ADLARITY TDS A and blue color indicates ADLARITY TDS B.



Source: M:\Donepezil_NDA212304_VS\Reviewer\Rscripts\pk_analysis_donepezil.R

Table 4-1: Bioequivalence assessment of primary PK parameters at steady-state for three formulations i.e. ARICEPT, ADLARITY TDS A and ADLARITY TDS B.

Treatment	n	Adjusted Geometric Mean[a]	Comparison	Adjusted GMR	90% CI[b,c]
$AUC_{0\text{-}168,ss}$ (h*ng/mL)					
TDS A	49	7646.7	TDS A/Oral C	1.040	(0.946, 1.144)
Oral C	53	7351.1			
TDS B	51	9475.8	TDS B/Oral C	1.289	(1.174, 1.416)
Oral C	53	7351.1			
$C_{max,ss}$ (ng/mL)					
TDS A	49	52.088	TDS A/Oral C	0.909	(0.825, 1.001)
Oral C	53	57.315			
TDS B	51	64.513	TDS B/Oral C	1.126	(1.024, 1.237)
Oral C	53	57.315			

Abbreviations: $AUC_{0\text{-}168,ss}$ = area under the plasma concentration-time curve during a 1-week period, at steady-state. For oral administration (Aricept 10 mg), $AUC_{0\text{-}168,ss}$ equals area under the plasma concentration-time curve from zero to 24 hours for Day 7 during steady-state Week 5 ($AUC_{0\text{-}24}$) x 7; CI = confidence interval; $C_{max,ss}$ = maximum observed plasma concentration over a dosage interval at steady-state; GMR = geometric mean ratio; LSM = least squares mean; Oral C = Aricept 10 mg/day; PK = pharmacokinetic(s); TDS = transdermal delivery system; TDS A = Corplex Donepezil TDS 105 cm^2 (10 mg/day donepezil); TDS B = Corplex Donepezil TDS 130 cm^2 (10 mg/day donepezil).

Note: Bioequivalence criteria are met if the 90% CI of the adjusted GMR for $AUC_{0\text{-}168,ss}$ and $C_{max,ss}$ are completely within the interval 0.80 to 1.25.

a. Adjusted geometric mean is the exponentiated LSM of the natural log-transformed values.

b. Estimates of the adjusted GMR confidence limits were exponentiated.

c. Analysis of variance using the natural logarithm of the PK parameter as the response variable; sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect.

Source: Corium clinical study report P-15086: Table 27, Page 121

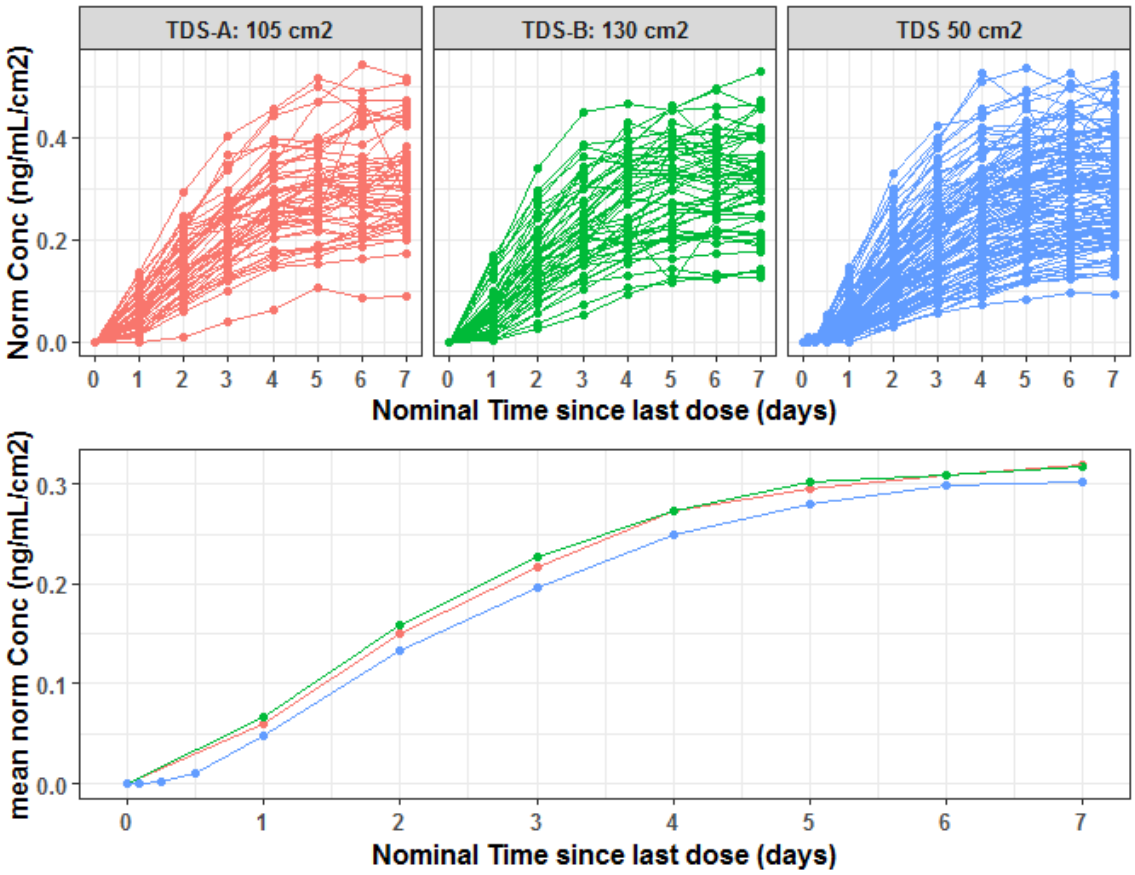
4.2.3 Dose Proportionality Assessment

Two approaches were used to evaluate dose proportionality between ADLARITY TDS 50 cm^2, ADLARITY TDS A and ADLARITY TDS B: (1) BE assessment of dose normalized PK parameters of three formulations; and (2) power model assessment of dose proportionality across three formulations. The summary of these two methods are provided below.

4.2.3.1 BE assessment of dose proportionality

In this analysis, dose proportionality between ADLARITY TDS A and ADLARITY TDS 50 cm^2; and between ADLARITY TDS B and ADLARITY TDS 50 cm^2 were assessed. Reviewer has evaluated the PK profiles of these formulations after adjusting for period effect (to correct for the residual exposure from previous treatment periods) and week-1 effect (to correct for the residual exposures from week-1) (**Figure 4-4**)..

Figure 4-4: Top row: Individual dose-normalized PK profiles of ADLARITY patch by dose (measured as cm^2); Bottom row: Median dose-normalized PK profiles of ADLARITY by dose. Red color indicates subjects with ADLARITY TDS A, green color indicates subjects with ADLARITY TDS B and blue color indicates subjects with ADLARITY TDS 50 cm^2.



Source: M:\Donepezil_NDA212304_VS\Reviewer\Rscripts\pk_analysis_donepezil.R

The sponsor has conducted BE analysis for assessing dose proportionality between ADLARITY TDS 50 cm^2, ADLARITY TDS A and ADLARITY TDS B. Briefly, the AUC_{0-168} and C_{max} for all three ADLARITY formulations were dose-normalized followed by analysis using linear mixed effect model to evaluate differences between these formulations. The BE criteria were achieved between ADLARITY TDS B and ADLARITY TDS 50 cm^2 for both C_{max} and AUC as well as between ADLARITY TDS A and ADLARITY TDS 50 cm^2 for C_{max} (**Table 4-2**). However, BE criteria was not met for ADLARITY TDS A and ADLARITY TDS 50 cm^2 for AUC_{0-168} [90% CI: (0.790, 0.902)]. Further analysis on dose proportionality was done using power model assessment

The reviewer was able to run the sponsor's analysis and obtained similar results as reported by the sponsor.

Table 4-2: Dose proportionality assessment between ADLARITY TDS 50 cm^2, ADLARITY TDS A and ADLARITY TDS B

Treatment	n	Adjusted Geometric Mean	Comparison	Adjusted GMR	90% CI[a]
$AUC_{0-168, DN}$ (h*ng/mL*cm^2)					
Lead-in TDS 5 mg[b]	54	28.614	Lead-in TDS 5 mg (50 cm^2)/ TDS A 10 mg (105 cm^2)	0.844	(0.790, 0.902)
TDS A 10 mg[c]	51	33. 910			
Lead-in TDS 5 mg[b]	55	31.328	Lead-in TDS 5 mg (50 cm^2)/ TDS B 10 mg (130 cm^2)	0.927	(0.868, 0.991)
TDS B 10 mg[d]	51	33.790			
$C_{max, DN}$ (ng/mL*cm^2)					
Lead-in TDS 5 mg[b]	54	0.285	Lead-in TDS 5 mg (50 cm^2)/ TDS A 10 mg (105 cm^2)	0.879	(0.826, 0.935)
TDS A 10 mg[c]	51	0.325			
Lead-in TDS 5 mg[b]	55	0.310	Lead-in TDS 5 mg (50 cm^2)/ TDS B 10 mg (130 cm^2)	0.973	(0.914, 1.035)
TDS B 10 mg[d]	51	0.318			

Abbreviations: $AUC_{0-168,DN}$ = area under the plasma concentration-time curve from Time 0 to 168 hours (dose-normalized) in Week 1 and Week 2 (only for TDS application), CI = confidence interval, $C_{max,DN}$ = maximum observed plasma concentration (dose-normalized) in Week 1 and Week 2 (only for patch application), GMR = geometric mean ratio; TDS = transdermal delivery system; TDS A = Corplex Donepezil TDS 105 cm^2 (10 mg/day donepezil); TDS B = Corplex Donepezil TDS 130 cm^2 (10 mg/day donepezil), TDS = transdermal delivery system.

a. Estimates of the GMR confidence limits were exponentiated.
b. Lead-in TDS = 5 mg/day Corplex Donepezil TDS (50 cm^2) applied at Hour 0 on Day 1 (Week 1).
c. TDS A 10 mg = 10 mg/day Corplex Donepezil TDS (105 cm^2) applied at Hour 0 on Day 1 (Week 2).
d. TDS B 10 mg = 10 mg/day Corplex Donepezil TDS (130 cm^2) applied at Hour 0 on Day 1 (Week 2).

Source: Corium clinical study report P-15086: Table 28, Page 123

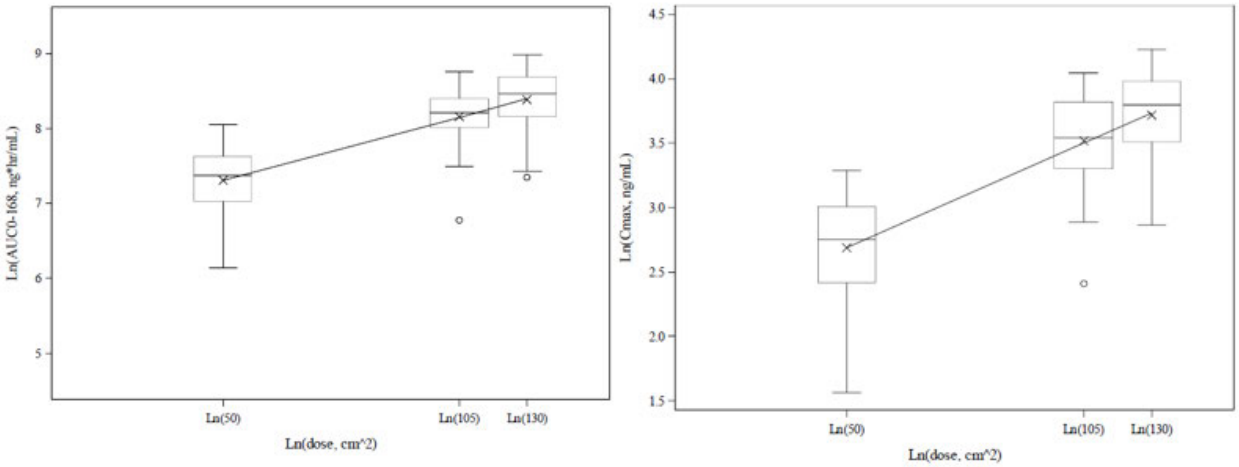
4.2.3.2 Power model assessment of dose proportionality

In the second approach, sponsor has used power model to provide an overall assessment of dose proportionality across the dose range of ADLARITY patch. The analysis was based upon PK parameters obtained separately from baseline-corrected plasma donepezil concentrations during Week 1 and baseline- and Week 1-corrected concentrations during Week 2.

A linear relationship between the natural log-transformed PK parameter (AUC_{0-168} and C_{max}) and natural log-transformed dose was assumed, where dose is the drug area (cm^2) of the ADLARITY patch. Estimates of the intercept (β_0) and slope (β_1) of the linear relationship were obtained from a linear mixed effect model and used to predict dose-normalized PK parameter for different doses (**Figure 4-5**). The model-predicted dose-normalized mean ratio and 90% CIs were assessed with respect to BE criteria. ADLARITY TDS B met BE criteria for both AUC_{0-168} and C_{max} which suggests dose proportionality from ADLARITY TDS 50 cm^2 to ADLARITY 130 cm^2 including ADLARITY TDS 105 cm^2 (**Table 4-3**).

The reviewer was able to run the sponsor's analysis and obtained similar results as reported by the sponsor.

Figure 4-5: Left plot: relationship between AUC_{0-168} and TDS Size following administration of ADLARITY patch ranging in size from 50 cm^2 to 130 cm^2 ; Right plot: relationship between C_{max} and TDS Size (bottom plot) following administration of ADLARITY patch ranging in size from 50 cm^2 to 130 cm^2.



Source: Corium power model assessment PK report: Figure 1 and 2, Page 13 and 14

Table 4-3: Result of power model to assess the dose proportionality for ADLARITY TDS 50 cm^2 and ADLARITY TDS B 130 cm^2

PK Parameter (unit)	TDS Size (cm^2)	n	Parameter Estimates: $ß_0$ (90% CI) $ß_1$ (90% CI)[a]	Model-predicted Dose Normalized Geometric Mean[b]	R_{DNM} (90% CI)[c]
$AUC_{0-168,ADJ}$ (ng*hr/mL)	130	47	2.8 (2.47, 3.20) 1.14 (1.07, 1.22)	34.00	0.87 (0.82, 0.93)
	50	94[d]		29.70	
$C_{max,ADJ}$ (ng/ml)	130	47	-1.57 (-1.89, -1.26) 1.09 (1.03, 1.16)	0.32	0.92 (0.87, 0.97)
	50	94		0.30	

CI = confidence interval

[a] Estimates of the intercept (β_0) and slope (β_1) of the linear relationship between the natural log (ln) transformed dose and the natural log transformed PK parameter. Estimates are from a linear mixed model using the ln of the PK parameter as the response variable, dose (continuous) as a fixed effect, and subject as a random effect. An unstructured covariance matrix was used.

[b] The model-predicted dose-normalized geometric mean for each dose is $\exp[\beta_0 + \beta_1 \cdot \ln(\text{dose})]/\text{dose}$.

[c] R_{DNM} = ratio of model-predicted dose-normalized means (TDS 50 cm^2 / TDS 130 cm^2) divided by r, where r = 50 / 130. An R_{DNM} of 1.00 denotes ideal dose proportionality. The 90% CI for the difference in ln-transformed means was calculated within the mixed linear model. Exponentiation of each confidence interval limit and division by r gave the 90% CI for R_{DNM}.

[d] Includes the Week 1 TDS 50 cm^2 lead-in patch application for the TDS 105 cm^2 and the TDS 130 cm^2 patches.

Source: Corium power model assessment PK report: Table S1, Page 4

Conclusion: Dose proportionality was established from ADLARITY TDS 50 cm^2 to ADLARITY 130 cm^2 including ADLARITY TDS 105 cm^2 using power model assessment.

4.2.4 Switching Strategy Assessment

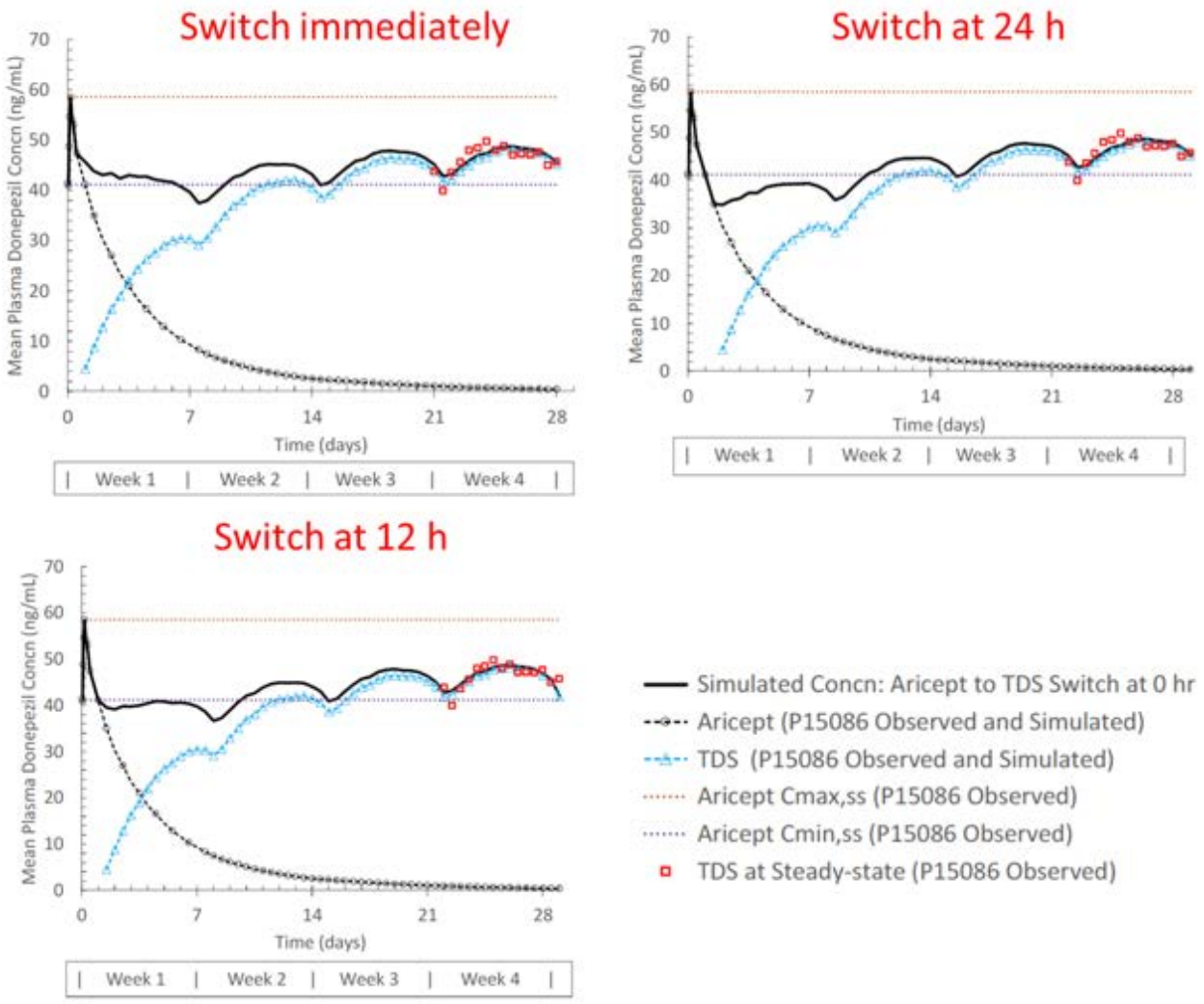
4.2.4.1 Sponsor Analysis

Sponsor has performed PK simulations using nonparametric superposition to assess the switching from daily oral ARICEPT at steady-state to weekly ADLARITY patch. Briefly, the mean PK profile of ADLARITY TDS A was added to the mean steady-state PK profile of the oral ARICEPT 10 mg at 0 h (immediately), 12 h and 24 h after the last oral dose administration (**Figure 4-6**). The resulting concentrations were lower than the observed mean steady-state C_{min} of oral ARICEPT (i.e. $C_{min,ss}$ = 41.2 ng/mL) for all three TDS switching scenarios (**Figure 4-7**). Specifically, the minimum concentration for immediate oral-to-TDS switch was 37.5 ng/mL attained at Day 8 after the last oral dose. For oral-to-TDS switch at 12 h after the last dose, the minimum concentration was 36.6 ng/mL attained at Day 8 after the last oral dose. The minimum concentration for oral-to-TDS switch at 24 h after the last dose was 34.9 ng/mL attained at Day 2 after the last oral dose. The oral-to-TDS switch within 24 h resulted in concentrations lowered by 15% with respect to oral $C_{min,ss}$ (**Figure 4-7**).

(b) (4)

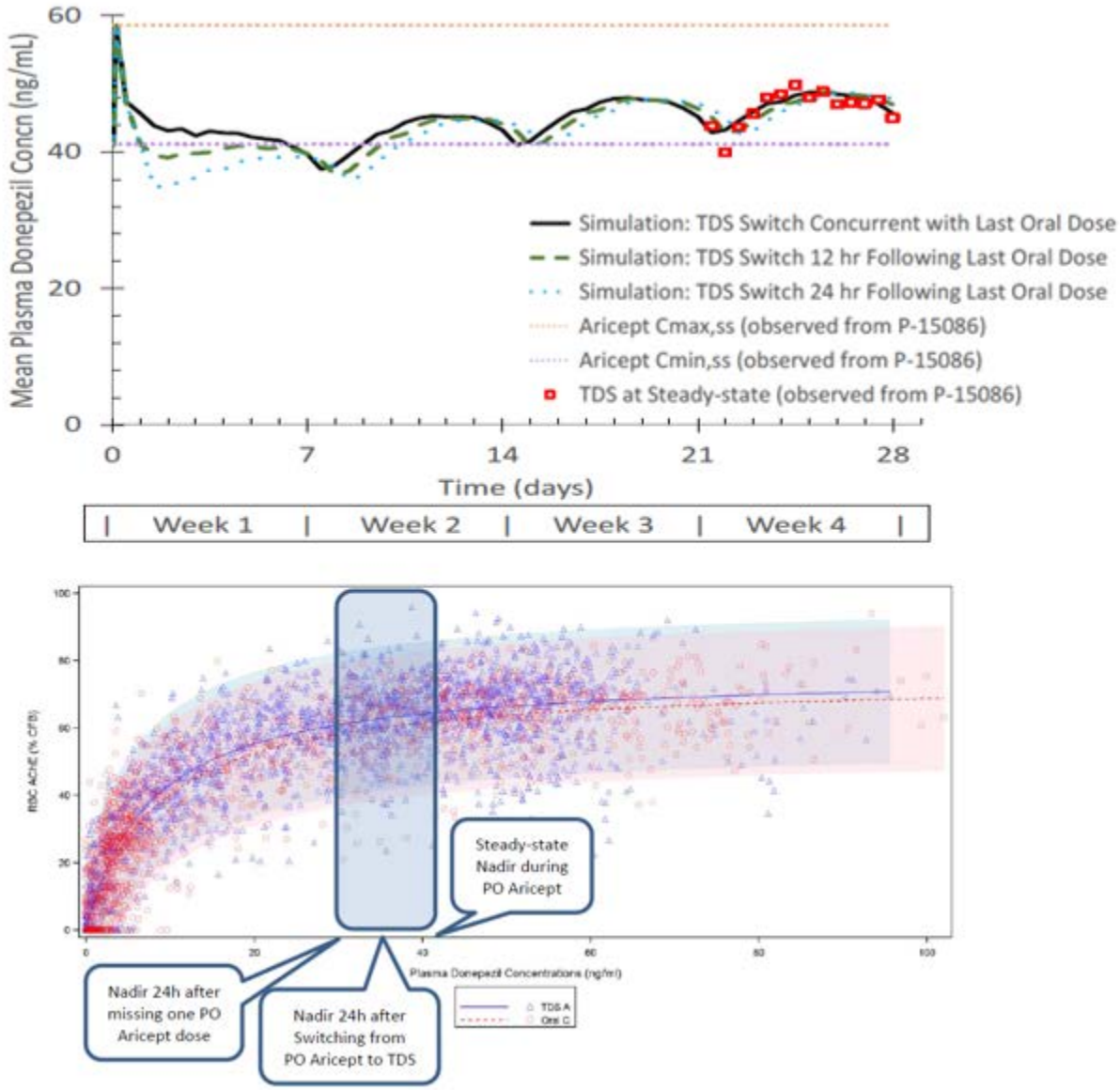
(**Figure 4-7**).

Figure 4-6: Mean PK profiles for the last ARICEPT dose at steady-state (black dashed line), first four once-weekly ADLARITY patch (cyan dashed line), and the non-parametric superposition simulations for switch from 10 mg/day ARICEPT to 10 mg/day once-weekly ADLARITY patch at 0h (left plot), 12h (middle plot) and 24h (right plot) after the last oral dose.



Source: Corium dose switching PK report: Appendix 11.1, 11.2 and 11.3; Page 17, 18 and 19

Figure 4-7: Top row: Mean PK profiles of donepezil for switch from 10 mg/day ARICEPT at steady-state to 10 mg/day once-weekly ADLARITY patch; Bottom row: Scatterplot of individual time-paired values of RBC AChE inhibition vs donepezil concentrations for ADLARITY (blue color) and ARICEPT (red color) across all sampling times (Study P-15086) along with the superimposed fit and confidence interval bands from the Hill model.



Source: Corium dose switching PK report: Figure 1 and 2, Page 14 and 15.

The reviewer has further investigated sponsor's inferences because of the following reasons:

1. The sponsor has only compared the minimum concentrations achieved after the oral-to-TDS switch with oral $C_{min,ss}$.

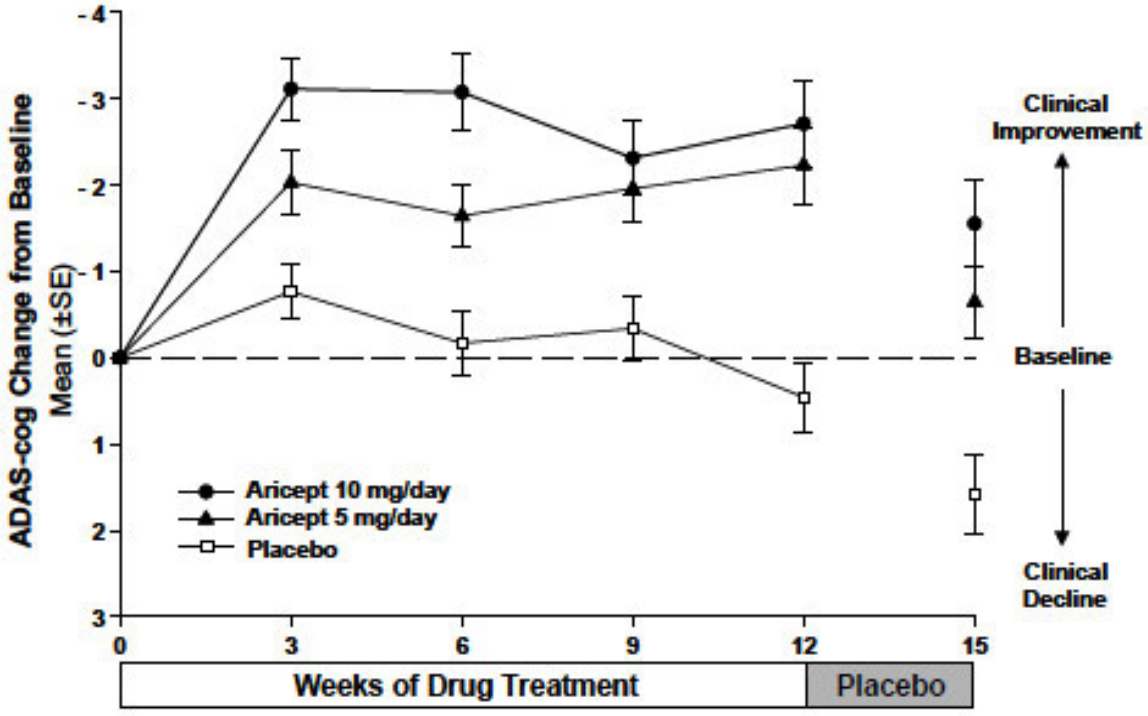
2. There is no established relationship between AChE inhibition and primary clinical endpoint i.e. ADAS-cog score.

The reviewer evaluated the impact of these minimum concentrations observed during the first ~10 days after oral-to-TDS switch using the dose-response information from ARICEPT label. The time-course of the ΔADAS-cog score for patients completing 15-week study (including 12 weeks of active/placebo treatment + 3 weeks of placebo washout) is shown in **Figure 4-8**, suggesting that:

1. The differences in ΔADAS-cog score between 5 mg/day and 10 mg/day at Week 12 were not statistically significant.
2. Following 3-week washout, the improvements in ADAS-cog score for both 5 mg/day and 10 mg/day ARICEPT declined by ~73%. Considering the plasma half-life of 70 h, plasma levels of donepezil will decrease by 99% following 3-week washout.

The above findings were used to understand the impact of lower concentrations after oral-to-TDS switch for 5 mg/day and 10 mg/day dose of donepezil.

Figure 4-8: Time-course of the change from baseline in ADAS-cog score for patients completing the 15-week Study.

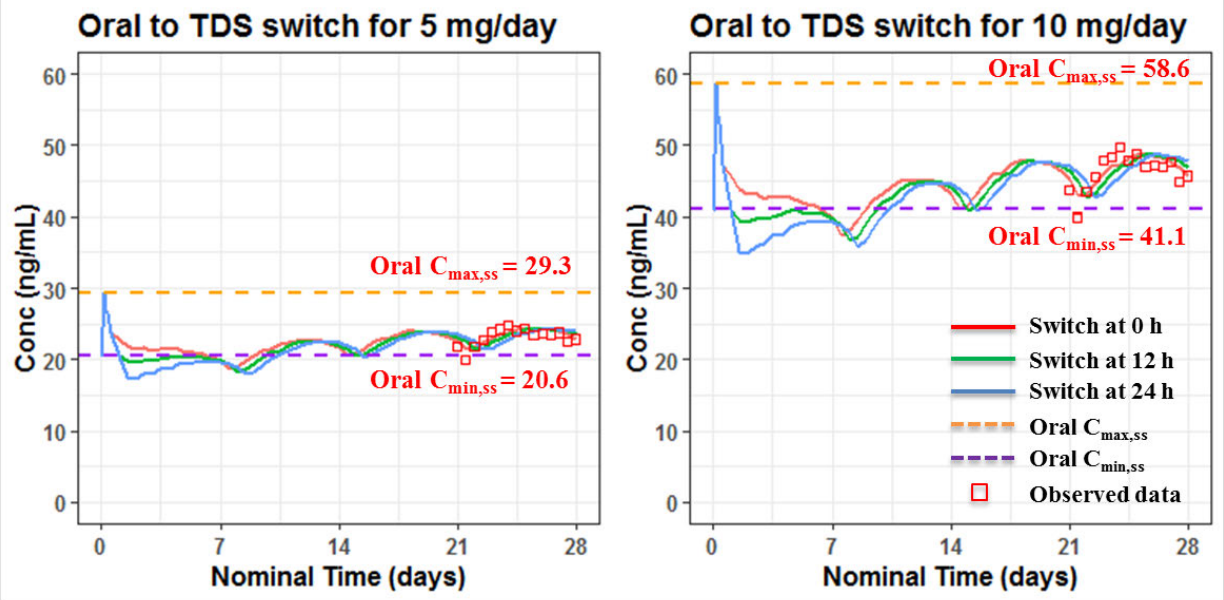


Source: ARICEPT label section 14.1

4.2.4.2 Reviewer Analysis

The reviewer was able to generate similar PK profiles and table summary as reported by the sponsor (**Figure 4-9**). Overall, the concentrations resulting from oral-to-TDS switch takes around 2 weeks to be within the range of oral $C_{max,ss}$ and $C_{min,ss}$. Additionally, the oral-to-TDS switch within 24 h resulted in concentrations lower by 41% and 15% with respect to oral $C_{max,ss}$ and $C_{min,ss}$ (**Figure 4-9**).

Figure 4-9: Top row: Mean PK profiles of 5 mg/day and 10 mg/day donepezil at steady-state after oral-TDS switch; Bottom row: Table summarizing the minimum concentrations resulting from three scenarios of oral-to-TDS switch for 5 mg/day and 10 mg/day dose. The minimum concentrations were attained on Day 7, Day 8 and Day 2 for the switch at 0 h, 12 h, and 24 h respectively.



Oral-to-TDS switching	5 mg/day: minimum conc [ng/mL]	10 mg/day: minimum conc [ng/mL]	Max reduction in conc (%)	
			w.r.t. $C_{max,ss}$	w.r.t. $C_{min,ss}$
At 0 h	18.7	37.5	36	9
At 12 h	18.3	36.6	38	11
At 24 h	17.4	34.9	41	15

Source: M:\Donepezil_NDA212304_VS\Reviewer\Rscripts\pk_analysis_donepezil.R

The reviewer has performed further analysis to compare overall PK profiles of donepezil after oral-to-TDS switch for both 10 mg/day and 5 mg/day dose. Briefly, the PK profiles were simulated for the repeat dose of oral ARICEPT 5 mg/day and 10 mg/day at steady-state using non-parametric

superposition. The simulated PK profiles were then compared with the PK profiles resulting from the oral-to-TDS switch at 24 h for both 5 mg/day and 10 mg/day donepezil dose (**Figure 4-10**).

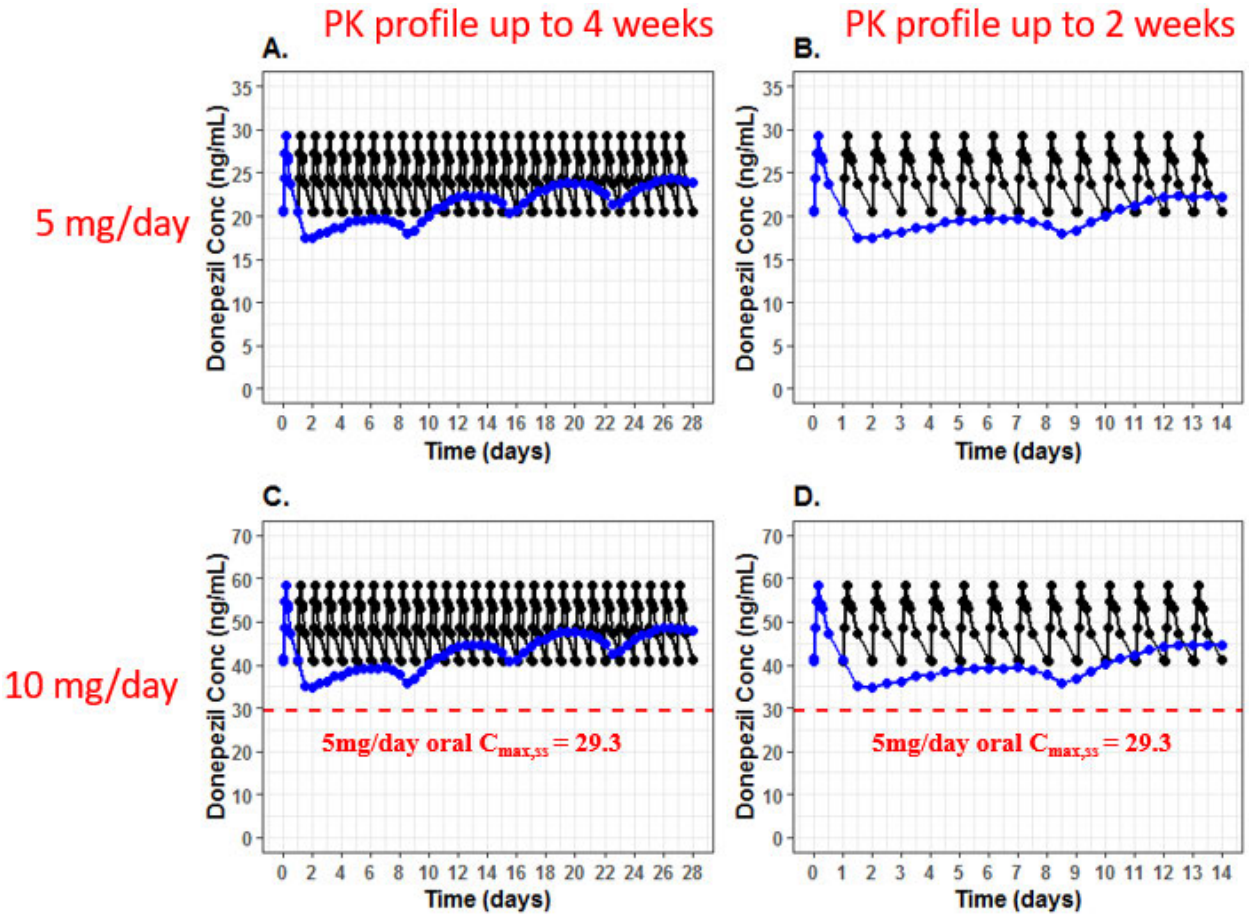
Oral-to-TDS switch for 10 mg/day treatment:

For 10 mg/day treatment, donepezil concentrations during the first 10 days after oral-to-TDS switch were lower by 41% relative to oral $C_{max,ss}$. However, these concentrations were higher than the maximum steady-state concentrations of 5 mg/day donepezil treatment (i.e. $C_{max,ss}$ = 29.3 ng/mL) (***Figure 4-10*** **C and D**). Since, both 5 mg/day and 10 mg/day ARICEPT have shown similar clinical benefit (**Figure 4-8**), patients after oral-to-switch for 10 mg/day within 24 h should continue to have clinical benefit.

Oral-to-TDS switch for 5 mg/day treatment:

For 5 mg/day treatment, donepezil concentrations during the first 10 days after oral-to-TDS switch were lower than oral $C_{min,ss}$ of 20.6 ng/mL (**Figure 4-10 A and B**). The clinical relevance of these lower concentrations is not known and to ensure clinical benefit, oral supplementation with 5 mg/day ARICEPT may be required during the first 2 weeks of oral-to-TDS switch.

Figure 4-10: (A): Comparison of PK profiles after repeat dosing of ARICEPT and oral-to-TDS switch for 5 mg/day dose; (B): Comparison of PK profiles up to 2 weeks after repeat dosing of ARICEPT and oral-to-TDS switch for 5 mg/day dose; (C): Comparison of PK profiles after repeat dosing of ARICEPT and oral-to-TDS switch for 10 mg/day dose; (D): Comparison of PK profiles up to 2 weeks after repeat dosing of ARICEPT and oral-to-TDS switch for 10 mg/day dose. Black color indicates repeat daily dosing of oral ARICEPT at steady-state and blue color indicate oral-to-TDS switch at 24 h after the last oral dose.



Source: M:\Donepezil_NDA212304_VS\Reviewer\Rscripts\pk_analysis_donepezil.R

Conclusions for oral-to-TDS switch:

- A patient who is being treated with a total daily dose of 10 mg of oral donepezil can be switched to the once-weekly 10 mg/day ADLARITY patch within 24 h after the last oral dose.
- A patient who is being treated with a total daily dose of 5 mg of oral donepezil can be switched to the once-weekly 5 mg/day ADLARITY patch within 24 h after the last oral dose. However, oral supplementation of 5 mg/day may be required during the first 2 weeks of oral-to-TDS switch.

4.2.5 Listing of Analysis Codes and Output Files

File Name	Description	Location
pk_analysis_donepezil.R	Exploratory PK analysis	\\Reviews\Donepezil_NDA212304_VS\Reviewer\Rscripts
be_analyis.sas	BE assessment	\\Reviews\Donepezil_NDA212304_VS\Reviewer\Rscripts
dose_prop_analysis.sas	Dose proportionality	\\Reviews\Donepezil_NDA212304_VS\Reviewer\Rscripts
power_analyis.sas	Power model assessment	\\Reviews\Donepezil_NDA212304_VS\Reviewer\Rscripts

4.2.6 References

1. Corium clinical study report P-15086: A phase 1, randomized, open-label, 3-way crossover, pilot, pharmacokinetic study to evaluate the steady-state pharmacokinetics of a once-weekly application of Corplex™ donepezil transdermal delivery system compared to daily oral administration of ARICEPT® in healthy adult subjects.
2. PK report: Power model assessment of dose proportionality of the corplex donepezil TDS results from Corium study P-15086.
3. PK report: Pharmacokinetic simulation of steady-state plasma donepezil concentrations for switch from daily oral ARICEPT® tablets to weekly administration of Corplex donepezil TDS using mean concentration results from Corium study P-15086.
4. ARICEPT label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020690s042,021720s014,022568s011lbl.pdf

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HRISTINA DIMOVA
05/28/2020 03:38:28 PM

VISHNU D SHARMA
05/28/2020 04:01:08 PM

VENKATESH A BHATTARAM
05/28/2020 05:02:50 PM

YUXIN MEN
05/28/2020 05:39:38 PM