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APPLICATION NUMBER:

212304Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212304
Supporting document:	1
Applicant's letter date:	September 30, 2019
CDER stamp date:	September 30, 2019
Product:	ADLARITY® (donepezil transdermal system)
Indication:	Treatment of mild, moderate, and severe Alzheimer's disease
Applicant:	Corium, Inc.
Review Division:	Neurology 1
Reviewer:	David B. Hawver, Ph.D.
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1 Executive Summary

1.1 Introduction

ADLARITY is a weekly transdermal delivery system (TDS) designed to deliver 5 or 10 mg donepezil per day continuously over the 7-day application period to patients with dementia of the Alzheimer's type.

1.2 Brief Discussion of Nonclinical Findings

The local toxicity of ADLARITY (Corplex Donepezil TDS) was assessed in three pivotal studies: a 39-week chronic dermal toxicity study in minipig, a 7-day primary skin irritation study in rabbit, and a skin sensitization study in guinea pig.

In the pivotal 39-week dermal toxicity study in minipig, application of Corplex Donepezil TDS (1, 2, or 4 10 mg/day patches per animal per week) or placebo (4 patches per animal per week) resulted in skin irritation (very slight to well-defined erythema, occasionally with very slight edema) at the site of application, with increased incidence and severity observed in the donepezil group. Moderate to severe erythema was rarely observed, and no irritation was observed in recovery animals by 24 hours after removal of the final patch. Histopathology evaluation showed increases in the severity of hyperkeratosis, rete pegs, and mononuclear cell infiltration at the application sites in donepezil groups compared to placebo or untreated groups and dose-dependent increases in the incidence and severity of mononuclear cell infiltration in untreated skin sites. Minimal to mild mononuclear cell infiltration in skin of the application site remained increased in HD animals compared to placebo and untreated groups after the 6-week recovery period. Other differences observed included increased final body weight (18% M, 5.7% F) and increased serum globulin (55% M, 42% F) at the HD.

In the 7-day primary skin irritation study in rabbit, application of Corplex Donepezil TDS 10 mg/day patches resulted in a Primary Irritation score of 1.4, slightly higher than that observed in the placebo patch-treated animals (1.0). Both were considered to be slight irritants.

In the skin sensitization study in guinea pigs, no evidence of delayed dermal contact sensitization was observed in animals challenged with 6-hour applications of Corplex Donepezil TDS 10 mg/day or placebo patches, 14 days after a 3-week induction period with Corplex Donepezil TDS 10 mg/day or placebo patch squares applied for 6 hours three times per week.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data submitted adequately support the approval of ADLARITY for the treatment of patients with Alzheimer's disease.

1.3.3 Labeling

The sponsor's proposed labeling for the nonclinical sections has not yet been reviewed.

2 Drug Information

2.1 Drug

CAS Registry Number
120011-70-3 (donepezil hydrochloride)

Generic Name
Donepezil Transdermal Delivery System (TDS)

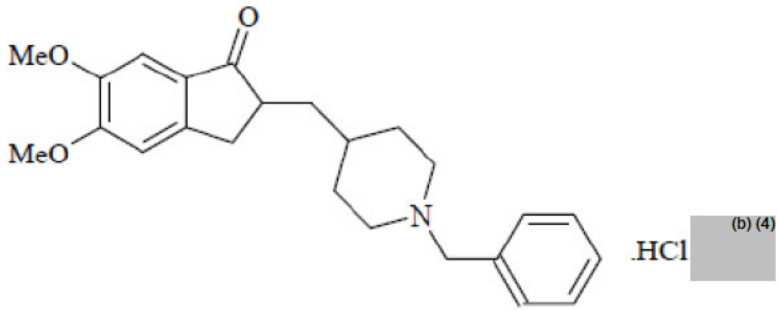
Proprietary Name
ADLARITY®

Chemical Name
1H-Inden-1-one, 2,3-dihydro-5,6-dimethoxy-2-((1-(phenylmethyl)-4-piperidinyl) methyl)-, hydrochloride

Molecular Formula
$C_{24}H_{29}NO_3 \cdot HCl$ (b) (4)

Molecular Weight
(b) (4)

Structure



(b) (4)

Pharmacologic Class
Acetylcholinesterase inhibitor

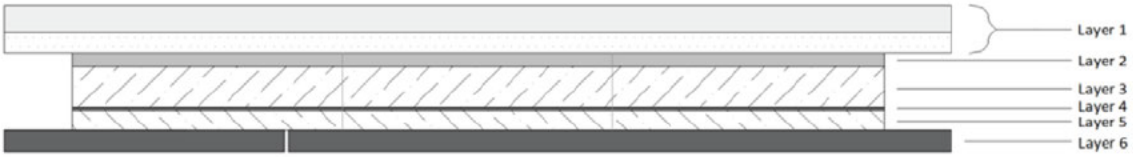
2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 129778 Corplex Donepezil TDS for the treatment of dementia of the Alzheimer's type

2.3 Drug Formulation

The 5- and 10-mg/day ADLARITY formulations are identical except for size—active areas are 52.5 $cm^2$and 105 cm^2, respectively). The TDS consists of six layers: a tan overly backing/adhesive layer, a separating layer, a microporous membrane layer, a skin contact adhesive layer, and a peel-off release liner. The drug matrix layer is (b) (4) The order and composition of the six layers of the TDS are shown in Figure 1 and Table 1, respectively.

Figure 1 Cross-Sectional View of the Corplex Donepezil TDS (Not to Scale)



Layer 1: Overlay Backing/Adhesive
Layer 2: Separating Layer
Layer 3: Drug Matrix
Layer 4: Microporous Membrane
Layer 5: Contact Adhesive
Layer 6: Release Liner (Removed at the time of use)

(page 3 of Quality Overall Summary)

Table 1 Composition of Corplex Donepezil TDS 5 mg/day and 10 mg/day Drug Product Strengths

Functional Layer (Layer No.)	Chemical Name of Excipient/Component	Quality Standard	Function	TDS Composition % (w/w) (1)
Overlay Backing/ Adhesive (Layer 1)	(b) (4)			
Separating Layer (Layer 2)				
Drug Matrix (Layer 3)				
Microporous Membrane (Layer 4)				
Contact Adhesive (Layer 5)				
Functional Layer (Layer No.)				
Release Liner (Layer 6)				

(b) (4)

(1) % (w/w) is based on the weight of individual layers and does not include overlay with (b) (4) separating layer, microporous membrane and release liner weights.

(pages 4-5 of Quality Overall Summary)

2.4 Comments on Novel Excipients

Three excipients, (b) (4) (an acrylate (b) (4) copolymer (b) (4)), triethyl citrate, and sorbitan monolaurate have not been used in transdermal products previously approved by FDA. Several other excipients are present at levels that exceed those listed in the FDA's Inactive Ingredient Database for transdermal administration. However, safety concerns have been addressed by providing adequate controls of the raw materials together with qualifying nonclinical studies of the TDS formulation.

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern have been identified.

2.6 Proposed Clinical Population and Dosing Regimen

ADLARITY is to be administered to patients with mild, moderate, or severe Alzheimer's disease via once-weekly application of the patch to the back, with at least 14 days between removal and re-application to the same skin site. The recommended starting dose is one 5 mg/day patch per week, with escalation to one 10 mg/day patch per week, if needed, to occur after 4 to 6 weeks of once-weekly dosing using the 5 mg/day patch.

2.7 Regulatory Background

A Pre-IND background package submitted on February 29, 2016, included questions regarding the development of Corplex Donepezil TDS for the treatment of Alzheimer's disease under IND 129778. As reflected in the written responses dated April 28, 2016, the sponsor was informed that the proposed rabbit primary irritation and guinea pig sensitization studies appeared sufficient to support the IND submission, that the planned nonclinical studies appeared sufficient to support a 505(b)(2) NDA, assuming no safety issues that would require additional nonclinical studies, and that the need for further characterization of proposed excipients would depend on the composition of the final clinical TDS formulation.

During an End-of-Phase-2 Meeting on August 23, 2017, the sponsor was informed that neither nonclinical photosafety nor ocular irritation studies of Corplex Donepezil TDS would be needed and that the need for additional nonclinical studies to assess the toxicity of the excipients would depend on the results of the 39-week study in minipig (see September 22, 2017, Minutes).

In a Pre-NDA meeting on September 6, 2018, the sponsor was informed that the nonclinical program appeared sufficient to support the submission of the NDA, unless the results of the 39-week study in minipig demonstrated that a dermal carcinogenicity study was needed (see October 4, 2018, Minutes).

3 Studies Submitted

3.1 Studies Reviewed

Pharmacokinetics

Pharmacokinetic Study of Donepezil following Bolus Intra Venous Administration in Female Gottingen Minipigs
(Corium Study TDS-042/P-16031; (b) (4))

Pharmacokinetic Study of Donepezil in Female Gottingen Minipigs following Oral Tablet and Transdermal Patch Administration
(Corium Study TDS-039/P-16020; (b) (4))

Validation Report for the Determination of Donepezil in Pig Plasma by Liquid Chromatographic Method with MS/MS Detection

([redacted]-VR16399)

Repeat-Dose Toxicology
Corplex™ Donepezil Transdermal Delivery System: A 39-Week Repeated-Dose Dermal Toxicity Study in Gottingen Minipigs
(Corium Study TDS-046/P-16041; [redacted])

Local Tolerance
ISO Skin Irritation Study in Rabbits
(Corium Study TDS-040; Formulation 1)

Modified ISO Skin Irritation Study in Rabbits (3 days)
(Corium Study TDS-044A)

Modified ISO Skin Irritation Study in Rabbits (7 days)
(Corium Study TDS-044B)

ISO Closed Patch Sensitization Study in Guinea Pigs
(Corium Study TDS-041; Formulation 1)

Modified ISO Closed Patch Sensitization Study in Guinea Pigs
(Corium Study TDS-044C)

Other
Bacterial Reverse Mutation Study with a Dose Range Finding Study
(Corium Study TDS-064; Potential leachable compound: [redacted])

3.1 Studies Not Reviewed

The following pharmacokinetic studies were not reviewed because they were conducted in Yorkshire pigs rather than in the pivotal toxicity species, Gottingen minipigs:

Non-GLP Pharmacokinetic Study of a Single Intravenous (IV) Administration of Donepezil HCl and Memantine HCl in Female Yorkshire Pigs
(Corium Study TDS-015)

Non-GLP Pharmacokinetic Analysis of Donepezil After Oral and Transdermal Patch Administration and Memantine After Oral Co-Administration in Female Pigs
(Corium Study TDS-018)

Non-GLP Pharmacokinetic Analysis of Donepezil Delivery in Pigs Following TDS Administrations
(Corium Study TDS-022)

Non-GLP Pharmacokinetic Study of a Single Oral Administration of 23 mg Aricept (Donepezil HCl) in Female Yorkshire Pigs
(Corium Study TDS-037)

The following local tolerance studies were not reviewed because they were non-GLP studies conducted with TDS formulations other than the final clinical formulation:

Modified ISO Skin Irritation Study in Rabbits
(Corium Study TDS-019; Formulation C)

Modified ISO Skin Irritation Study in Rabbits
(Corium Study TDS-024; Formulation F)

Modified ISO Closed Patch Sensitization Study in Guinea Pigs
(Corium Study TDS-023; Formulation C)

Modified ISO Closed Patch Sensitization Study in Guinea Pigs
(Corium Study TDS-023; Formulation F)

Modified ISO Skin Irritation Study in Rabbits
(Corium Study TDS-036; Formulation 1)

Modified ISO Skin Irritation Study in Rabbits
(Corium Study TDS-036; Formulation 2)

Modified ISO Skin Irritation Study in Rabbits
(Corium Study TDS-036; Formulation 3)

The following studies were not reviewed because extractables and leachables were reviewed by the CMC team:

Extractable and Leachable Testing for Corplex™ Donepezil Transdermal Delivery System (TDS)
((b) (4) Study 85378)

Evaluation of Leachables from Aged Drug Product (Corplex Donepezil TDS) Using Two Solvent Systems, and Analyses by UPLC-PDA and GC-MS
((b) (4) Study 86637)

Proposed Elemental Impurity Levels for the Corplex Donepezil Transdermal Delivery System
((b) (4))

Risk Assessment of Leachables from the Corplex Donepezil Transdermal Delivery System Backing, Release Liner, (b) (4) Membrane, (b) (4) and Pouch
((b) (4))

Corplex™ Donepezil TDS: Evaluation of Compounds Observed Above Monitoring Level in Controlled Extraction and Leachables Correlation Studies
((b) (4))

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Pharmacokinetic Study of Donepezil following Bolus Intra Venous Administration in Female Gottingen Minipigs
(Corium Study TDS-042/P-16031; [redacted] (b) (4); non-GLP)

Female Gottingen minipigs (N=6, 6 to 7 months old) were administered a single dose of donepezil HCl (1 mg/kg at 0.033 mL/kg in 0.9% saline) via bolus IV injection into the ear vein. Blood was collected predose and at 0.033, 0.083, 0.167, 0.333, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose for analysis of plasma donepezil concentrations.

Mean pharmacokinetic parameters and the concentration vs. time profile are shown in Table 1 and Figure 3 below, respectively.

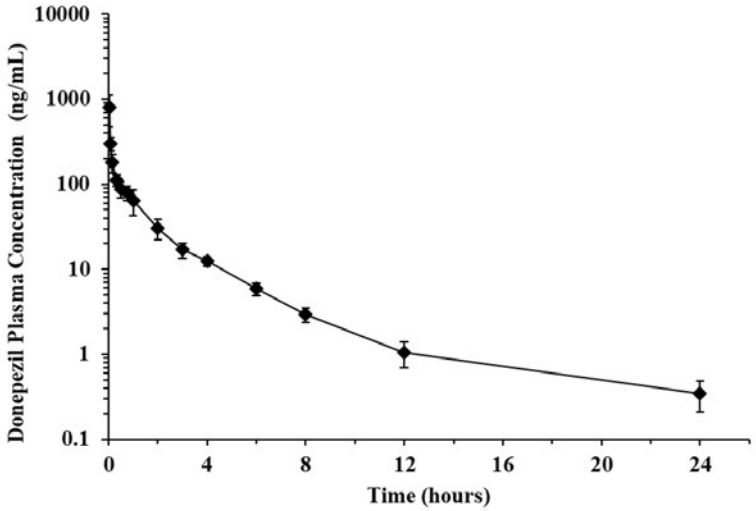
Table 1: Mean (±SD) and CV% Donepezil Pharmacokinetic Parameters on Day 1 Following a Single Bolus Intravenous Administration of 1 mg/kg Donepezil Hydrochloride to Female Minipigs

Dose (mg/kg)	Statistic	C_0 (ng/mL)	T_{last}[a] (hr)	AUC_{Tlast} (hr*ng/mL)	AUC_{0-48hr} (hr*ng/mL)	AUC_{INF} (hr*ng/mL)	Cl (mL/hr/kg)	V_z (mL/kg)	V_{ss} (mL/kg)	$T_{1/2}$ (hr)
1	N	6	6	6	6	5	5	5	5	5
	Mean	1640	24	297	301	309	3260	21700	6410	4.67
	SD	1030	(24 - 24)	37.5	36.7	30.1	300	5140	1480	1.26
	CV%	62.7	NA	12.7	12.2	9.74	9.23	23.7	23.1	26.9

NA- Not applicable
a: Median (minimum - maximum), median value only reported if it was an actual collection interval

(page 7 of Study Report)

Figure 3 Mean Plasma Donepezil Concentration-Time Profiles Following a Single Bolus Intravenous Administration of 1 mg/kg Donepezil Hydrochloride to Female Gottingen Minipigs (Mean ± SD; n = 6) [Sponsor Study No. TDS-042]



(page 12 of Pharmacokinetic Written Summary)

Pharmacokinetic Study of Donepezil in Female Gottingen Minipigs following Oral Tablet and Transdermal Patch Administration
(Corium Study TDS-039/P-16020; (b) (4); Corplex Donepezil TDS Formulation 1, Lot 36894B, 105 cm^2; GLP, QA)

Female Gottingen minipigs (N=6/grp) were administered Corplex Donepezil TDS and oral Aricept in a 2-way crossover design, with a 13-day washout period between dosing periods (see Table 1 below). The TDS Formulation 1 used in this study was identical to the final clinical formulation (i.e., that used in Bioequivalence Study P-15086), except that a different overlay adhesive was used. Blood samples were collected during, and for 3 days following, patch application, and for 3 days following oral administration of Aricept.

Table 1 Study Design for GLP Single Dose PK Evaluation of Corplex Donepezil TDS and Aricept Tablets in Female Gottingen Minipigs [Sponsor Study No. TDS-039]

Group ID	Dosage Form	Number of Animals	Dosing Route	Dose Administered
DOSING PHASE 1				
1	Corplex Donepezil TDS	6	Transdermal (1)	1 patch (2)
2	Corplex Donepezil TDS	6	Transdermal (1)	3 patches (2)
DOSING PHASE 2				
1	Aricept (donepezil HCl) tablet	6	Oral, one tablet	10 mg (3 animals) 23 mg (3 animals)
2	Aricept (donepezil HCl) tablet	6	Oral, one tablet	10 mg (3 animals) 23 mg (3 animals)

(1) Patches were applied to the shaved dorsal surface of each animal and left in place for seven consecutive days.
(2) Donepezil HCl content was 193.7 mg per patch

(page 8 of Pharmacokinetic Written Summary)

No drug- or patch-related adverse effects were observed. Slight, barely perceptible erythema, without edema, was observed at the TDS application site in 3/12 animals. Mean pharmacokinetic parameters and the concentration vs. time profiles are shown in the figures and tables below.

Figure 1 **Plasma Donepezil Concentration-Time Profiles Following a Single Administration of One or Three Corplex Donepezil TDS 7-Day Patches to Female Minipigs (Mean ± SD; n = 6/group) [Sponsor Study No. TDS-039]**

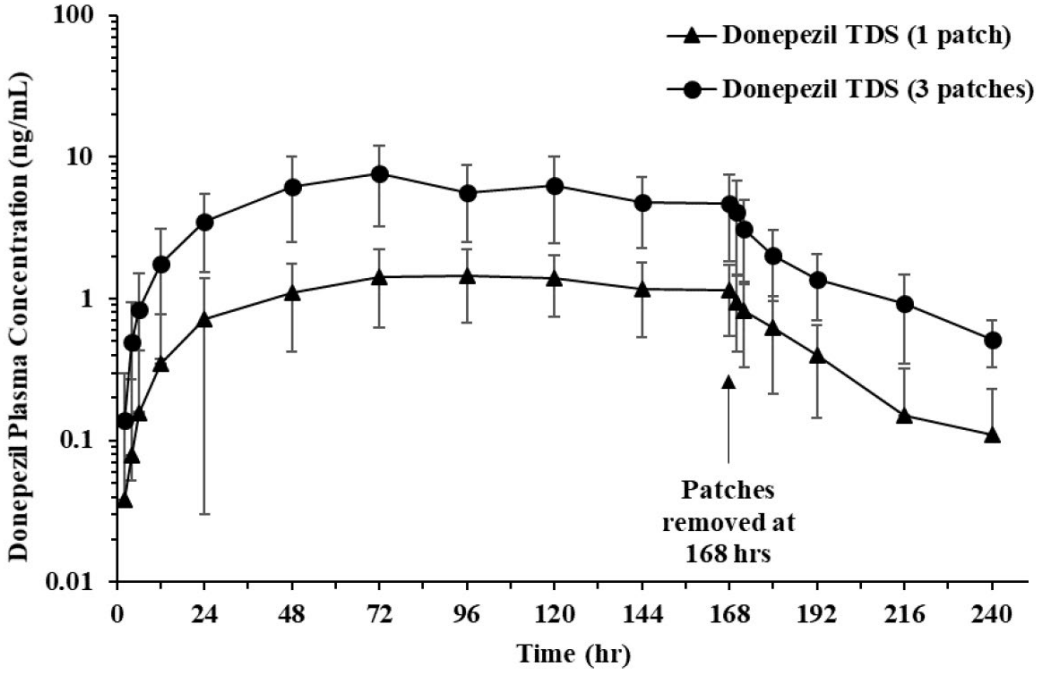


Table 2 **Pharmacokinetic Summary of Once-Weekly Corplex Donepezil TDS Applied at Two Dose Levels to Female Minipigs (Mean ± SD; n = 6/group) [Sponsor Study No. TDS-039]**

PK Parameter	Corplex Donepezil TDS (1 patch)	Corplex Donepezil TDS (3 patches)	Parameter Ratio (1)
t_{max} (hr) (2)	(72–120)	72 (72-120)	–
C_{max} (ng/mL)	1.57 ± 0.752	7.81 ± 4.34	4.97
$AUC_{0\text{-}168hr}$ (hr*ng/mL)	188 ± 102	871 ± 483	4.63
AUC_{last} (hr*ng/mL) (3)	211 ± 117	972 ± 528	4.61
$t_{1/2}$ (hr) (4)	26.0 ± 3.36	28.4 ± 11.2	1.09

(1) Ratio of the mean PK parameter values for 3 patches versus 1 patch.
(2) Median (range) for t_{max}. Median was only reported if it was an actual collection interval.
(3) For AUC_{last} calculations, t_{last} ranged from 170 to 240 hrs for the 1-patch group and was 240 hrs for all animals in the 3-patch group.
(4) n = 5 for both treatment groups (one animal in each group had insufficient data to determine half-life).

Figure 2 **Mean Plasma Donepezil Concentration-Time Profiles Following a Single Oral Administration of 10 or 23 mg Aricept Tablet to Fema Gottingen Minipigs (Mean ± SD; n = 6/group) [Sponsor Study No. TDS-039]**

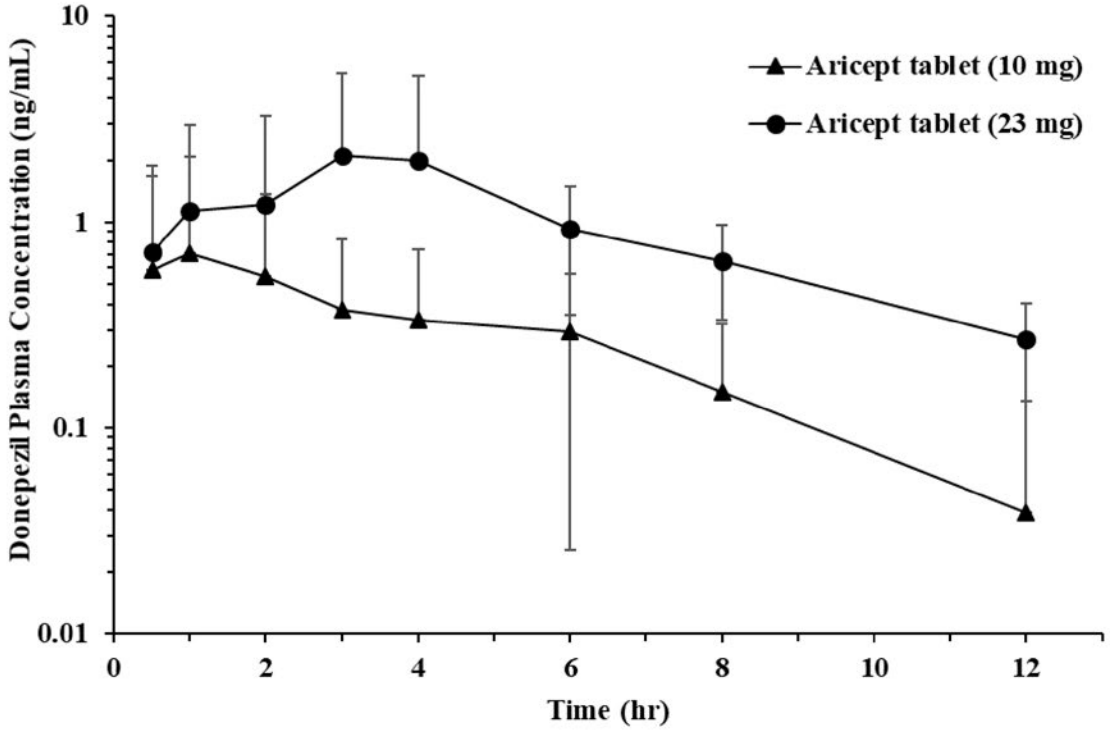


Table 3 **Pharmacokinetic Summary Following a Single Oral Administration of 10 or 23 mg Aricept Tablet to Female Gottingen Minipigs (Mean ± SD; n = 6/group) [Sponsor Study No. TDS-039]**

PK Parameter	Oral Aricept, 10 mg (1)	Oral Aricept, 23 mg	Parameter Ratio (2)
t_{max} (hr) (3)	4 (1–6)	(1-8)	–
C_{max} (ng/mL)	0.789 ± 1.32	2.91 ± 3.17	3.69
AUC_{last} (hr*ng/mL) (4)	4.67 ± 4.13	11.7 ± 10.7	2.51
$t_{1/2}$ (hr) (5)	2.36	2.74 ± 0.381	1.16

(1) Two of the six animals had concentrations that were below the limit of quantitation (BLQ) at every time point.
(2) Ratio of the mean PK parameter values for 23 mg dose versus 10 mg dose.
(3) Median (range) for t_{max}. Median was reported only if it was an actual collection interval.
(4) For AUC_{last} calculations, t_{last} ranged from 6 to 12 hrs for 10 mg and 8 to 12 hrs for 23 mg.
(5) Insufficient data points to determine half-life for some animals. n = 1 and n = 3 for 10 mg and 23 mg Aricept groups, respectively.

(pages 10-11 of Pharmacokinetic Written Summary)

Using information from the IV study of donepezil in minipig, absolute bioavailabilities for oral and TDS formulations were compared, as shown in Table 4 below:

Table 4 Donepezil Absolute Bioavailabilities for Single Dose Oral and Transdermal Administrations to Female Gottingen Minipigs (Mean ± SD) [Sponsor Study No. TDS-039 and TDS-042]

Treatment (1)	Dose (mg)	Dose/BW (mg/kg)	AUC_{last} (hr*ng/mL) (2)	BA (%) (3)
Intravenous bolus injection	16.1 ± 0.82 (4)	0.99 ± 0.0005 (4)	296.3 ± 37.6	–
Oral Aricept, 10 mg tablet	10	0.65 ± 0.03	4.67 ± 4.12	2.46 ± 2.24
Oral Aricept, 23 mg tablet	23	1.58 ± 0.06	11.7 ± 10.7	2.45 ± 2.21
Corplex Donepezil TDS, 1 patch	70 (5)	5.23 ± 0.32	211 ± 117	13.3 ± 6.85
Corplex Donepezil TDS, 3 patches	210 (5)	15.7 ± 1.11	973 ± 528	20.5 ± 10.8

BA = bioavailability; BW = body weight

(1) n = 6 for all treatments except 10 mg oral Aricept (n = 4)

(2) See Report R-17003 for individual intravenous AUC and BW values and Report R-17004 for individual transdermal patch and oral AUC and BW values. Mean and/or SD values for AUC may be slightly different from study reports due to rounding.

(3) %BA was calculated for individual animals, based on AUC_{last} and body weight normalized dose for individual animals, mean AUC_{last} and dose (mg/kg) for intravenous injection, and then averaged.

(4) IV dose based on volume administered and body weight (see Report R-17003 for individual volumes and body weights).

(5) TDS dose based on target delivered dose of 10 mg/day per patch and 7-day wear period.

(page 13 of Pharmacokinetic Written Summary)

In the TDS study, a 3-fold increase in dose (3 patches vs. 1 patch per animal) resulted in 4.6-fold, 4.6-fold, 4.4-fold, and 5.0-fold increases in $AUC_{0\text{-}240\ hr}$, $AUC_{0\text{-}168\ hr}$, AUC_{INF}, and C_{max}, respectively. Mean $t_{½}$ values were 26.0 hrs and 28.4 hrs following administration of 1 or 3 patches, respectively.

In the oral study, a 2.3-fold increase in dose (23 mg vs. 10 mg per animal) resulted in 3.9-fold, 1.8-fold, and 3.7-fold increases in $AUC_{0\text{-}72\ hr}$, AUC_{INF}, and C_{max}, respectively. Mean $t_{½}$ values were 2.36 hrs and 2.74 hrs following oral administration of 10 or 23 mg, respectively.

Absolute bioavailability was 5.4- to 8.4-fold greater after transdermal administration compared to oral administration.

5.2 Toxicokinetics

Toxicokinetic data were reviewed with the toxicity study in minipig.

5.3 Methods of Analysis

Validation Report for the Determination of Donepezil in Pig Plasma by Liquid Chromatographic Method with MS/MS Detection
([redacted]; GLP, QA)

The LC/MS/MS method used to determine the concentration of donepezil in plasma of Gottingen minipigs in the pivotal 39-week TDS study, as well as the IV, TDS, and oral PK studies described in Section 5.1 above, was validated over the concentration range of 0.204 to 99.833 ng/mL. Results met acceptance criteria for selectivity, precision, accuracy, freeze-thaw stability (up to 4 cycles), and room temperature stability (up to 6 hours).

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were submitted.

6.2 Repeat-Dose Toxicity

Corplex™ Donepezil Transdermal Delivery System: A 39-Week Repeated-Dose Dermal Toxicity Study in Gottingen Minipigs

Study no.:	Corium Study TDS-046/P-16041 (b) (4)
Study report location:	edr
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 26, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Corplex Donepezil TDS Patch (105 cm^2), 10 mg/day target delivered dose, Lot 37865, 96.9% of target 193.7 mg donepezil per patch

Key Study Findings

- The NOAEL was the high dose of 4 TDS/week (40 mg/day delivered donepezil).

Table A. Study Design

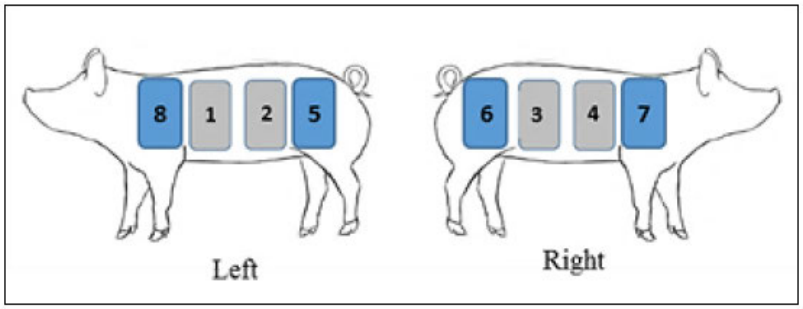
Group Number	Group Designation	Number of Patches	Estimated Transdermal Dose Level (mg/day)	Study Phase and Number of Animals: 12-Week Interim M	12-Week Interim F	39-Week Terminal M	39-Week Terminal F	6-Week Recovery M	6-Week Recovery F
1	Untreated	None	NA	2	2[c]	3	3	2	2
2	Placebo	4 Patches	0	2	2	5	5	3	3
3	Low Dose	1 Patch[a]	10	2	2	4	4	2	2
4	Mid Dose	2 Patches[a]	20	2[b]	2	4	4	2	2
5	High Dose	4 Patches[a]	40	2	2	5	5	3	3

M - Male, F – Female
[a]1, 2, and 4 patches represent 1x, 2x, and 4x the intended clinical dose. Each patch active delivery area was 105 cm^2 with a target delivered dose of 10 mg/day.
[b]Animal number 861 was found dead on Day 57.
[c]Animal number 810 was found dead on Day 27.

(page 10 of Study Report)

Methods:

Doses:	Untreated, 4 placebo patches, 1 donepezil patch, 2 donepezil patches, 4 donepezil patches (maximum feasible dose, based on size of patch and animal body surface area, allowing for application site rotation, if needed; see diagram below)
Frequency of dosing:	Weekly
Route of administration:	Each TDS patch was applied to one of 8 shaved skin sites on the dorsal surface (see diagram below) and covered with a secondary overlay (Medline SureSite 123 Transparent Film Dressing). Animals were wrapped with bandaging, secured with non-irritating semi-occlusive tape, and fitted with jackets. Untreated animals were shaved, wrapped, and jacketed, but no secondary overlay was applied. Patches were replaced if they became dislodged during the 7-day dosing period. Patches were rotated to alternate sites if skin irritation score of ≥ 2 was observed at the previous site.
Dose volume:	105 cm^2 containing (b) (4) mg donepezil per TDS
Formulation/Vehicle:	The to-be-marketed donepezil TDS was used Placebo TDS was similar, w/out donepezil
Species/Strain:	Gottingen Minipigs, (b) (4)
Number/Sex/Group:	See Table A above
Age:	5.5 to 8.5 months old
Weight:	12.5-16.3 kg M; 12.5-17.2 kg F
Satellite groups:	12-week interim, 6-week recovery
Unique study design:	Used patches removed at the end of TK weeks (Days 8, 29, 85, 183, and 274), or dislodged during TK weeks, were evaluated for residual donepezil content
Deviation from study protocol:	No deviations reported had an impact on the outcome or integrity of the study



(page 18 of Study Report)

Observations and Results

Local Dermal Toxicity

Dermal Irritation Scores

Each animal was evaluated for dermal irritation 30 minutes after patch removal using the Draize scale (Erythema: none [0], very slight [1], well-defined [2], moderate to severe [3], severe, to slight eschar formation [4]; Edema: none [0], very slight [1], slight [2], moderate [3], severe [4]). Recovery animals were evaluated immediately after patch removal, and at 0.5, 24, 48, 72, 96, 120, 144, and 168 hours after removal of the final patch.

Transient very slight to well-defined erythema was observed in all patch-treated groups, but incidence and severity were generally higher in donepezil groups than in the placebo group. Erythema scores of 3 to 4 were relatively rare, occurring in 0/13 untreated, 2/20 placebo, 1/16 LD, 3/16 MD, and 2/20 HD animals. Transient very slight edema was occasionally observed in a few animals in the placebo and donepezil groups. Slight edema was observed in some of the animals that had erythema scores of 3 to 4. Full reversibility of patch- and donepezil-related increases in dermal irritation was demonstrated by 24 hours after removal of the final patch in recovery animals. Dermal irritation was not considered adverse because it was transient, generally mild, and not related to dose or duration.

Mortality

Mortality was assessed twice daily.

No patch- or donepezil-related mortality was observed.

Clinical Signs

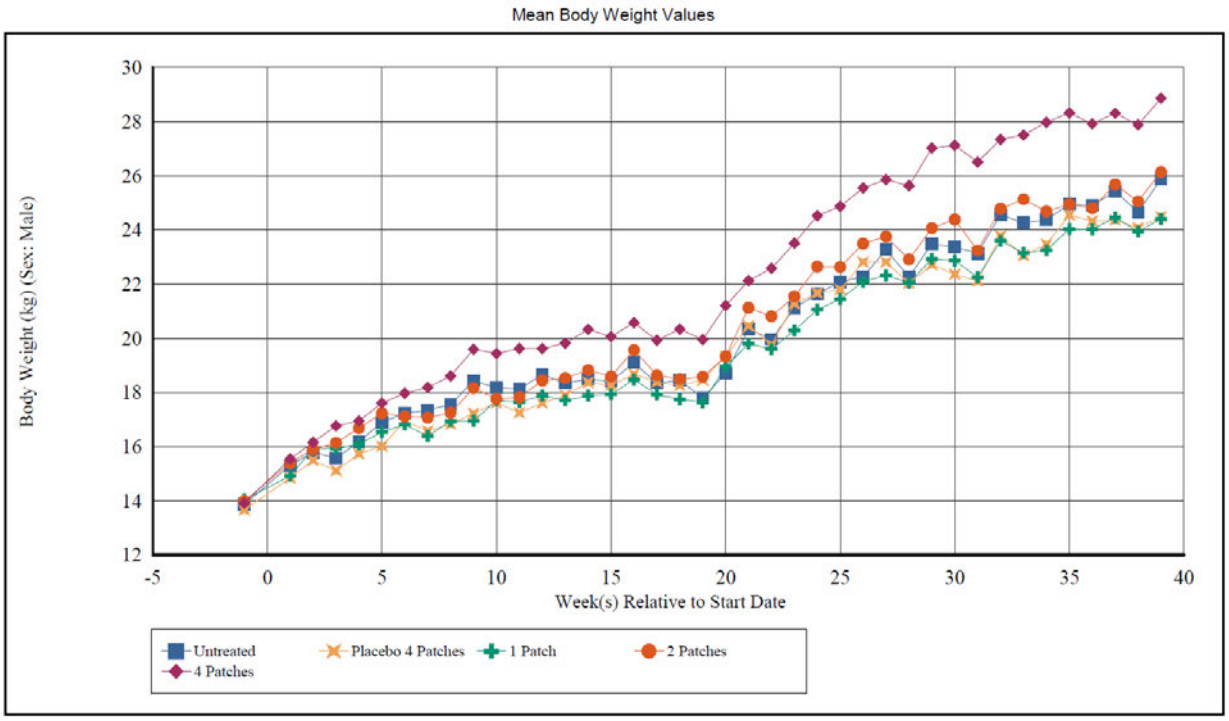
Detailed clinical examinations were conducted daily.

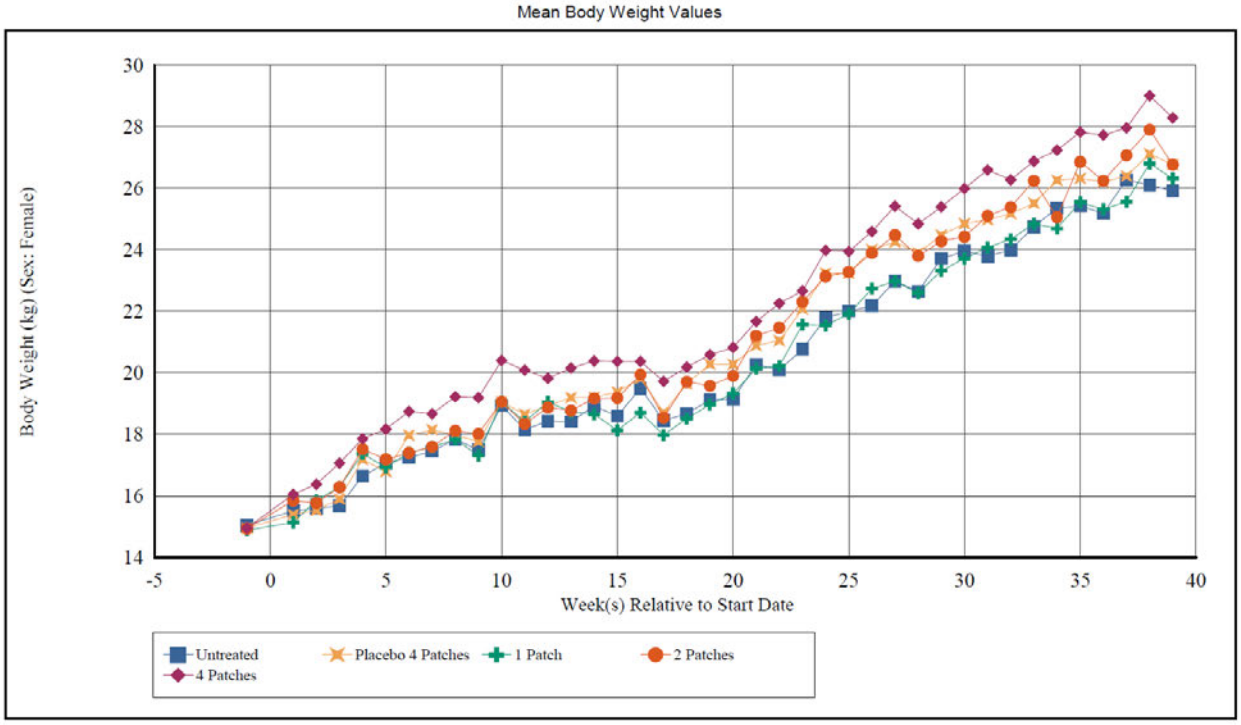
No patch- or donepezil-related effects were observed.

Body Weights

Body weight was assessed weekly.

As shown in the figures below, mean body weight was increased in HDM and HDF compared to placebo controls (18% and 5.7%, respectively in Week 39; 26% and 4.7%, respectively, following the 6-week recovery period).





(pages 112 -113 of Study Report)

Ophthalmoscopy

Ophthalmoscopic examinations were conducted prior to dosing initiation and prior to the interim, terminal, and recovery necropsies.

No patch- or donepezil-related effects were observed.

ECG

ECG examinations were conducted prior to dosing initiation and prior to the interim, terminal, and recovery necropsies.

No patch- or donepezil-related effects were observed.

Hematology and coagulation

Hematology and coagulation parameters were evaluated twice prior to dosing initiation and once prior to the interim, terminal, and recovery necropsies.

No patch- or donepezil-related effects were observed.

Clinical Chemistry

Clinical chemistry parameters were evaluated twice prior to dosing initiation and once prior to the interim, terminal, and recovery necropsies.

Globulin was consistently increased in placebo and donepezil groups (up to 55% M, 42% F, compared to baseline) at the 12-week, 39-week, and recovery time points. Albumin/globulin ratio was consistently decreased.

Urinalysis

Urinalysis parameters were evaluated twice prior to dosing initiation and once prior to the interim, terminal, and recovery necropsies.

No patch- or donepezil-related effects were observed.

Gross Pathology

Necropsy was performed on all animals found dead or euthanized at scheduled intervals.

Brown discoloration observed at most sites of patch application had no microscopic correlates and was completely reversible following the 6-week recovery period.

Organ Weights

Weights were recorded for the following organs: adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary gland, prostate gland, spleen, testes, thymus, thyroid gland, and uterus (with cervix).

No patch- or drug-related effects were observed.

Histopathology

Tissues from all animals in the placebo control and HD groups were examined microscopically. The following tissues were also examined in the MD and LD groups: brain, heart, kidneys, liver, sciatic nerve, skin (treated and untreated areas), spinal cord (cervical, thoracic, lumbar, and gross lesions. Only skin and gross lesions were examined in recovery groups. Wrapped and unwrapped skin areas from untreated main study and recovery group animals were also examined.

The battery of tissues examined was adequate. No Peer Review was conducted. A signed pathology report was provided.

Histological Findings

No consistent differences were seen between placebo and donepezil groups at the 12-week interim necropsy, except minimal epidermal hyperplasia at the application sites in MD and HD. As shown in Table J below, test article-related findings observed at the terminal necropsy included increases in the severity of hyperkeratosis, rete pegs, and mononuclear cell infiltration at the application sites in donepezil groups compared to placebo or untreated groups. The incidence and severity of mononuclear cell infiltration was dose-dependently increased in untreated skin sites.

Table J. Test Article-Related Microscopic Observations – 39 Week Terminal

Group	1		2		3		4		5	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	3	3	5	5	4	4	4	4	5	5
Skin, treated/wrapped[a]										
hyperkeratosis	0	1	5	5	4	4	4	4	5	5
-minimal	0	1	5	5	1	3	1	0	2	0
-mild	0	0	0	0	2	1	3	3	3	4
-moderate	0	0	0	0	1	0	0	1	0	1
increased rete pegs	0	0	5	5	4	4	4	4	5	5
-minimal	0	0	0	1	0	0	0	0	0	0
-mild	0	0	5	4	3	3	4	1	4	1
-moderate	0	0	0	0	1	1	0	3	1	4
infiltration, mononuclear cell, increased	0	0	5	5	4	4	4	4	5	5
-minimal	0	0	5	5	2	1	1	0	2	0
-mild	0	0	0	0	1	3	3	4	2	4
-moderate	0	0	0	0	1	0	0	0	1	1
Skin, untreated/unwrapped[b]										
infiltration, mononuclear cell, increased	0	0	0	2	0	1	2	3	4	3
-minimal	0	0	0	2	0	1	2	3	2	2
-mild	0	0	0	0	0	0	0	0	2	1

Group 1: Untreated
Group 2: Placebo 4 Patches
Group 3: 1 Patch
Group 4: 2 Patches
Group 5: 4 Patches

M: Male
F: Female
[a]Includes calls for both "Skin, treated" (Groups 2-5) and "Skin, wrapped" (Group 1) dorsal trunk sites.
[b]Includes calls for both "Skin, untreated" (Groups 2-5) and "Skin, unwrapped" (Group 1) forelimb and hindlimb sites.

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As shown in Table L below, the incidence and/or severity of patch-related findings observed at the application sites were reduced after the 6-week recovery period. The only remaining difference between donepezil and placebo application sites was increased minimal to mild mononuclear cell infiltration in the HD group.

Table L. Microscopic Observations – 6 Week Recovery

Group		1		2		3		4		5	
Sex		M	F	M	F	M	F	M	F	M	F
Number Examined		2	2	3	3	2	2	2	2	3	3
Skin, treated/wrapped[a]											
hyperkeratosis		0	1	3	2	1	1	1	2	3	3
	-minimal	0	1	3	2	1	1	1	2	3	1
	-mild	0	0	0	0	0	0	0	0	0	2
increased rete pegs		2	2	3	3	2	2	2	2	3	3
	-minimal	1	2	1	0	0	0	1	0	1	2
	-mild	1	0	2	3	2	2	1	2	2	1
infiltration, mononuclear cell, increased		0	0	0	1	0	0	0	1	2	2
	-minimal	0	0	0	1	0	0	0	1	1	2
	-mild	0	0	0	0	0	0	0	0	1	0
erosion/ulcer											
	-minimal	0	0	0	1	0	0	0	0	0	0
exudate, epidermal surface		0	1	3	3	2	2	2	2	2	3
	-minimal	0	1	1	2	1	2	2	2	1	2
	-mild	0	0	2	1	1	0	0	0	1	1
Skin, untreated/unwrapped[b]											
hyperkeratosis		2	2	3	1	2	2	1	1	1	3
	-minimal	1	1	3	0	1	2	1	1	1	3
	-mild	1	1	0	1	1	0	0	0	0	0
increased rete pegs		1	1	3	2	2	2	1	1	2	2
	-minimal	0	1	3	2	0	1	1	1	2	2
	-mild	1	0	0	0	2	1	0	0	0	0
infiltration, mononuclear cell, increased		0	0	0	0	1	0	0	0	0	0
	-minimal	0	0	0	0	0	0	0	0	0	0
	-mild	0	0	0	0	1	0	0	0	0	0
hyperplasia, epidermal											
	-minimal	0	0	0	0	0	0	0	0	0	1
exudate, epidermal surface		1	2	1	2	2	1	1	2	0	1
	-minimal	1	1	1	2	2	0	1	1	0	0
	-mild	0	1	0	0	0	1	0	1	0	1

Group 1: Untreated
Group 2: Placebo 4 Patches
Group 3: 1 Patch
Group 4: 2 Patches
Group 5: 4 Patches

M: Male
F: Female
[a]Includes calls for both "Skin, treated" (Groups 2-5) and "Skin, wrapped" (Group 1) dorsal trunk sites.
[b]Includes calls for both "Skin, untreated" (Groups 2-5) and "Skin, unwrapped" (Group 1) forelimb and hindlimb sites

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Toxicokinetics

Blood samples were collected from all animals predose on Day 1; at 2, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours after patch application on Days 1, 22, 78, and 167; at 24 hours after application on Day 176; and at 2, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours after removal of the final patch on Day 267. Plasma donepezil concentrations were assessed in untreated and placebo controls predose and 24 hours after the first patch application on Day 1 and 24 hours after the final patch removal on Day 267, and in drug-treated groups at all time points.

Donepezil was not detected in pre-dose samples or in any samples from untreated or placebo controls. Donepezil concentration vs. time curves, toxicokinetic parameters, and apparent delivered doses are shown in the tables below:

Table P. Mean Donepezil Toxicokinetic Parameters for Weeks 1, 4, 12, and 39 (Days 1, 22, 78, and 267)

Group	Patch Application Week (Day)	C_{max} (ng/mL)	$AUC_{0\text{-}168hr}$ (hr*ng/mL)	Accumulation Ratio (R)[a]	Female to Male Ratio (F:M)[b]
Males					
Group 3: 10 mg/day (1 patch)	1 (1)	1.53	167	NA	NA
	4 (22)	5.71	506	4.07	NA
	12 (78)	6.95	431	2.89	NA
	39 (267)	5.61	297	2.35	NA
Group 4: 20 mg/day (2 patches)	1 (1)	3.13	333	NA	NA
	4 (22)	7.90	657	1.82	NA
	12 (78)	11.3	731	2.62	NA
	39 (267)	7.10	411	1.33	NA
Group 5: 40 mg/day (4 patches)	1 (1)	5.68	608	NA	NA
	4 (22)	9.77	882	1.64	NA
	12 (78)	10.5	820	1.66	NA
	39 (267)	7.95	505	1.06	NA
Females					
Group 3: 10 mg/day (1 patch)	1 (1)	1.98	223	NA	1.34
	4 (22)	4.70	427	2.66	0.844
	12 (78)	4.57	314	1.74	0.729
	39 (267)	2.21	158	0.708	0.534
Group 4: 20 mg/day (2 patches)	1 (1)	4.00	450	NA	1.35
	4 (22)	12.0	996	2.50	1.52
	12 (78)	7.29	562	1.33	0.769
	39 (267)	15.8	808	1.65	1.97
Group 5: 40 mg/day (4 patches)	1 (1)	8.14	874	NA	1.44
	4 (22)	21.7	1800	2.05	2.04
	12 (78)	14.8	1160	1.36	1.41
	39 (267)	13.4	792	0.963	1.57

a: R = $AUC_{0\text{-}168hr\ Day\ 22,\ Day\ 78,\ or\ Day\ 267}/AUC_{0\text{-}168hr\ Day\ 1}$ [calculated for individual animals, then averaged]
b: F:M Ratio = Mean $AUC_{0\text{-}168hr\ Female}$/Mean $AUC_{0\text{-}168hr\ Male}$
NA – Not applicable

(page 41 of Study Report)

Table 7 **Mean Donepezil Exposure Adjusted for Body Weight Gain and Associated Ratios Following Repeated Application of Corplex Donepezil TDS in Gottingen Minipigs for 39 Weeks [Sponsor Study No. TDS-046]**

Patch Application Day/Week	Sex	$AUC_{0\text{-}168hr,\ BW\ Adjusted}$ (1) (hr*ng/mL) Number of Patches (3)			Body Weight-Adjusted AUC Ratios (2) Number of Patches (3)		
		1	2	4	1	2	4
1/1	M	167	333	607	1.0	2.0	3.6
22/4		545	708	964	1.0	1.3	1.8
78/12		518	859	1039	1.0	1.7	2.0
267/39		482	673	927	1.0	1.4	1.9
1/1	F	223	450	874	1.0	2.0	3.9
22/4		492	1108	2017	1.0	2.3	4.1
78/12		394	679	1419	1.0	1.7	3.6
267/39		274	1355	1368	1.0	4.9	5.0

BW = body weight; M = male; F = female

(1) $AUC_{0\text{-}168hr,\ BW\ Adj} = AUC_{0\text{-}168hr}$ x BW Ratio [BW Ratio = BW(Week t)/BW(Week 1), where t = 1, 4, 12, and 39 weeks.]

(2) BW Adjusted AUC Ratio = Mean $AUC_{0\text{-}168hr,\ BW\ Adj\ 1\ patch,\ 2\ patches,\ 4\ patches}$/Mean $AUC_{0\text{-}168hr,\ BW\ Adj\ 1\ patch}$

(3) Target doses for 1, 2, and 4 patches were 10, 20, and 40 mg/day, respectively.

(page 16 of Pharmacokinetic Written Summary)

Analysis of Residual Drug in Patch (Study R-18034)

Table 8 **Weekly and Daily Apparent Dose Delivered of Donepezil HCl During Weeks 4 and 39 Following Once Weekly Corplex Donepezil TDS Administration of 1, 2, and 4 Patches (10, 20, and 40 mg/day, Respectively) to Male and Female Gottingen Minipigs* [Sponsor Study No. TDS-046]**

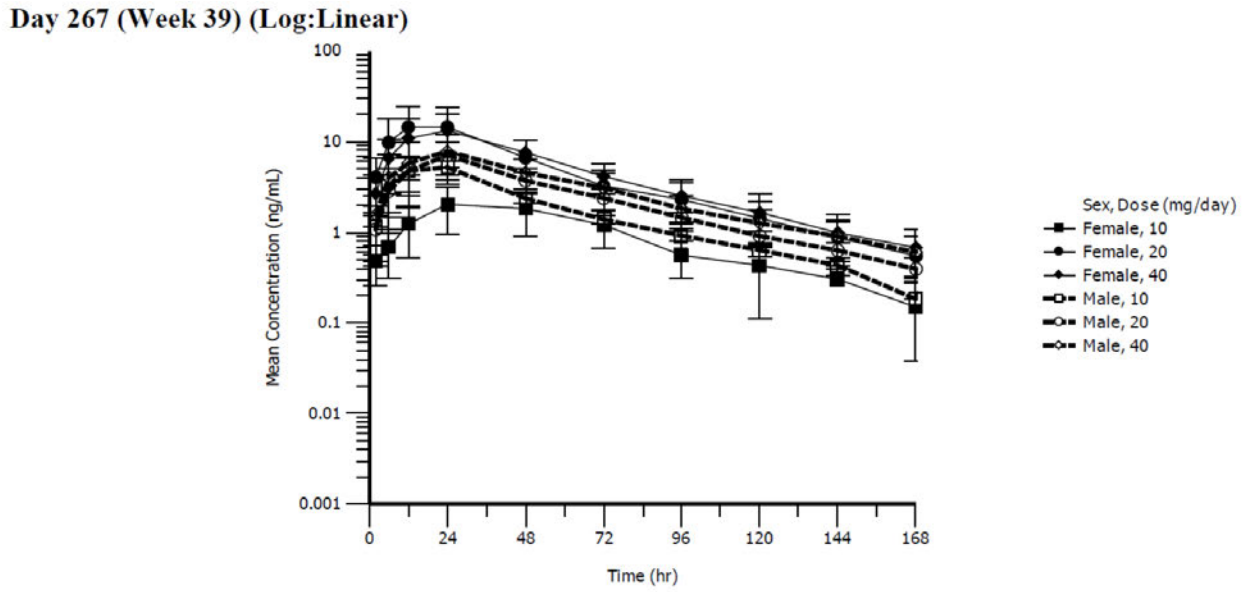
Group No.	Treat-ment	Target Daily Dose (mg/day)	Target Weekly Dose (mg)	Sex	Apparent Weekly Dose (mg) (1) Week 4	Apparent Weekly Dose (mg) (1) Week 39	Apparent Daily Dose (mg/day) (2) Week 4	Apparent Daily Dose (mg/day) (2) Week 39
3	1 patch	10	70	M	NA	(b) (4)	NA	(b) (4)
				F	NA		NA	
4	2 patches	20	140	M	NA		NA	
				F	NA		NA	
5	4 patches	40	280	M				(b) (4)
				F				

*Mean ± SD; n = 10 minipigs (Week 4); n = 8 minipigs (Week 39); NA = not analyzed

(1) Apparent Dose Delivered = Mean Content in Unused Control Patches – Residual Drug in Patch. Apparent Weekly Dose is the sum of the apparent doses for each patch applied to the animal. The average of the sums for each treatment group is reported in the table.

(2) Apparent Daily Dose = Apparent Weekly Dose ÷ 7.

(page 19 of Pharmacokinetic Written Summary)



Donepezil plasma exposures (C_{max} and $AUC_{0\text{-}168hr}$) generally increased proportionally with dose, with the following exceptions: no increase was seen in HDM compared to MDM on Day 78, a 5- to 7-fold increase occurred with the 2-fold dose increase in MDF compared to LDF on Day 279, and no increase was observed in HDF compared to MDF on Day 279. Exposures in F tended to be slightly (1.4- to 2-fold) higher than in M in MD and HD groups. Median T_{max} values were generally 24 to 48 hrs postdose. Donepezil concentrations steadily decreased approximately 30 to 90% over the 5 to 6 days following the peak. After removal of the final patch, mean $t_{½}$ values were 12.4 hrs, 11.9 hrs, and 14.6 hrs in HDM (N=1), MDF (N=1), and HDF (N=3), respectively.

As noted in the statements below, failure of the patches to remain adhered to the application site for the full 7-day period may have contributed to the lower than expected delivered doses and exposures observed in the HD group.

> "One reason for the lower than expected apparent doses for the 4-patch group could be inconsistent patch adhesion. For the high dose group, patches were most often applied to Sites 1, 2, 3, and 4 on the animals, as shown in [the diagram in the Methods section above]. During Week 4, several patches required replacement due to inconsistent adhesion. Patch lifting and detachment were most often observed for Sites 2 and 3, which were located over the abdomen near the rear legs, areas with a great amount of movement. The two sites were typically only protected by a transparent adhesive dressing, which did not always adhere well, because the bandaging and jacket usually shifted forward over time during the wear period. In contrast, Sites 1 and 4 (the sites also used for the 1- and 2-patch groups) were located over the rib cage, always uniformly covered by the bandage and jacket, and remained well adhered." *(page 8 of Study Report R-18034)*

8 Carcinogenicity

The carcinogenic potential of systemic donepezil was adequately assessed in the oral carcinogenicity studies in mouse and rat described in the labeling for Aricept. A dermal carcinogenicity study is not needed because the 39-week study of Corplex Donepezil TDS in minipig did not show drug- or patch-related effects (e.g., neoplastic or preneoplastic changes) that would warrant such a study.

10 Special Toxicology Studies

ISO Skin Irritation Study in Rabbits
(Corium Study TDS-040; (b) (4); initiated July 14, 2016; Corplex Donepezil TDS 10 mg/day, Formulation 1, Lot 36894B, (b) (4) mg donepezil/105 cm^2 active patch area; Placebo patch, Formulation 1, Lot 36941; GLP, QA)

The Corplex Donepezil TDS formulation used in this study was identical to the final clinical donepezil TDS formulation (i.e., that used in Bioequivalence Study P-15086), except that a different adhesive was used in the overlay.

Duplicate 25 mm x 25 mm squares of Corplex Donepezil TDS and placebo patch (cut to include 250 mm^2 the 1-cm wide overlay border and 375 mm^2 of the active area) and negative control (gauze) were applied in duplicate to the skin of each of 3 male New Zealand White (NZW) rabbits and left in place for 72 hours. Skin sites were evaluated for irritation (erythema and edema) at 1, 24, 48, and 72 hours after removal of the patch.

Very slight to moderate erythema, without edema, was observed at the sites treated with Corplex Donepezil TDS. The Primary Irritation score was 2.6—moderate irritant.

Well-defined to moderate erythema, without edema, was observed at the sites treated with placebo patch. The Primary Irritation score was 2.1—moderate irritant.

No erythema or edema was observed at the sites treated with gauze.

Modified ISO Skin Irritation Study in Rabbits (3 days)
(Corium Study TDS-044A; (b) (4); initiated July 6, 2017; Corplex Donepezil TDS 10 mg/day, Lot 37865, (b) (4) mg donepezil/105 cm^2 active patch area; Placebo patch, Lot 37921; GLP, QA)

The Corplex Donepezil TDS formulation used in this study was identical to the final clinical donepezil (i.e., that used in Bioequivalence Study P-15086).

Duplicate 25 mm x 25 mm squares of Corplex Donepezil TDS and placebo patch (cut to include 250 mm^2 the 1-cm wide overlay border and 375 mm^2 of the active area) and negative control (gauze) were applied in duplicate to the skin of each of 3 male NZW

rabbits and left in place for 72 hours. Skin sites were evaluated for irritation (erythema and edema) at 1, 24, 48, and 72 hours after removal of the patch.

None to severe erythema, with none to well-defined edema, was observed at the sites treated with Corplex Donepezil TDS. The Primary Irritation score was 2.8—moderate irritant.

None to severe erythema, without edema, was observed at the sites treated with placebo patch. The Primary Irritation score was 1.8—slight irritant.

No erythema or edema was observed at the sites treated with gauze.

Modified ISO Skin Irritation Study in Rabbits (7 days)
(Corium Study TDS-044B; (b) (4); initiated July 6, 2017; Corplex Donepezil TDS 10 mg/day, Lot 37865, (b) (4) mg donepezil/105 cm^2 active patch area; Placebo TDS, Lot 37921; GLP, QA)

The Corplex Donepezil TDS formulation used in this study was identical to the final clinical donepezil (i.e., that used in Bioequivalence Study P-15086).

Duplicate 25 mm x 25 mm squares of Corplex Donepezil TDS and placebo patch (cut to include 250 mm^2 the 1-cm wide overlay border and 375 mm^2 of the active area) and negative control (gauze) were applied in duplicate to the skin of each of 3 female NZW rabbits and left in place for 7 days. Skin sites were evaluated for irritation (erythema and edema) at 1, 24, 48, and 72 hours after removal of the patch.

None to moderate erythema, without edema, was observed at the sites treated with Corplex Donepezil TDS. The Primary Irritation score was 1.4—slight irritant.

None to well-defined erythema, without edema, was observed at the sites treated with placebo patch. The Primary Irritation score was 1.0—slight irritant.

No erythema or edema was observed at the sites treated with gauze.

ISO Closed Patch Sensitization Study in Guinea Pigs
(Corium Study TDS-041; (b) (4); initiated July 14, 2016; Corplex Donepezil TDS 10 mg/day, Formulation 1, Lot 36894B, (b) (4) mg donepezil/105 cm^2 active patch area; Placebo patch, Formulation 1, Lot 36941; GLP, QA)

The Corplex Donepezil TDS formulation used in this study was identical to the final clinical donepezil TDS formulation (i.e., that used in Bioequivalence Study P-15086), except that a different adhesive was used in the overlay.

Duplicate 25 mm x 25 mm squares of Corplex Donepezil TDS and placebo patch (cut to include 250 mm^2 the 1-cm wide overlay border and 375 mm^2 of the active area) and

negative control (gauze) were applied the skin of the left flank of female Hartley guinea pigs (N=10 donepezil, 10 placebo, 5 negative control) for 6 hours, three times per week for 3 weeks during the induction period.

Fourteen days after the final induction application, donepezil-induced animals were challenged with 25 mm x 25 mm squares of donepezil and negative control applied to the skin of the right flank dorsal and ventral regions, respectively; placebo-induced animals were challenged with 25 mm x 25 mm squares of placebo and negative control applied to the skin of the right flank dorsal and ventral regions, respectively; and negative control-induced animals were challenged with 25 mm x 25 mm squares of donepezil and placebo control applied to the skin of the right flank ventral regions, while negative control squares were applied to the skin right flank dorsal region. Patches were removed 6 hours later, and skin sites were evaluated 24 and 48 hours later for skin reactions, using the following scale: 0—no visible change, 1—discrete or patchy erythema, 2—moderate and confluent erythema, or 3—intense erythema and swelling.

All scores for all sites on all animals were 0. No evidence of delayed dermal contact sensitization was observed under the conditions tested.

Modified ISO Closed Patch Sensitization Study in Guinea Pigs
(Corium Study TDS-044C; (b) (4); initiated July 6, 2017; Corplex Donepezil TDS 10 mg/day, Lot 37865, (b) (4) mg donepezil/105 cm^2 active patch area; Placebo TDS, Lot 37921; GLP, QA)

The Corplex Donepezil TDS formulation used in this study was identical to the final clinical donepezil (i.e., that used in Bioequivalence Study P-15086).

Duplicate 25 mm x 25 mm squares of Corplex Donepezil TDS and placebo patch (cut to include 250 mm^2 the 1-cm wide overlay border and 375 mm^2 of the active area) and negative control (gauze) were applied the skin of the left flank of male Hartley guinea pigs (N=10 donepezil, 10 placebo, 5 negative control) for 6 hours, three times per week for 3 weeks during the induction period.

Fourteen days after the final induction application, donepezil-induced animals were challenged with 25 mm x 25 mm squares of negative control and donepezil applied to the skin of the right flank dorsal and ventral regions, respectively; placebo-induced animals were challenged with 25 mm x 25 mm squares of negative control and placebo applied to the skin of the right flank dorsal and ventral regions, respectively; and negative control-induced animals were challenged with 25 mm x 25 mm squares of donepezil and placebo control applied to the skin of the right flank ventral regions, while negative control squares were applied to the skin right flank dorsal region. Patches were removed 6 hours later, and skin sites were evaluated 24 and 48 hours later for skin reactions, using the following scale: 0—no visible change, 1—discrete or patchy erythema, 2—moderate and confluent erythema, or 3—intense erythema and swelling.

All scores for all sites on all animals were 0. No evidence of delayed dermal contact sensitization was observed under the conditions tested.

Bacterial Reverse Mutation Study with a Dose Range Finding Study
(Corium Study TDS-064; (b) (4); initiated April 5, 2019; Potential leachable compound: (b) (4); GLP, QA)

A potential leachable compound, (b) (4), was identified in the extractables and leachables assessment and detected at a level higher than the threshold for toxicological concern for potentially mutagenic impurities (1.5 µg/day). Therefore, this compound was tested in a bacterial reverse mutation assay at up to 5000 µg per plate using four *S. typhimurium* strains (TA98, TA100, TA1535, and TA1537) and one *E. coli* strain (WP2*uvr*A), with and without rat liver S9 metabolic activation, using standard methods.

No increases in the number of revertant colonies were observed in any strain compared to the negative control. Therefore, (b) (4) was non-mutagenic under the conditions tested.

11 Integrated Summary and Safety Evaluation

Corplex Donepezil TDS is a 6-layer patch designed to deliver 5 mg (52.5 cm^2 patch) or 10 mg (105 cm^2 patch) donepezil per day continuously during the 7-day wear period. The local toxicity of this product was assessed in three pivotal studies: a 39-week chronic dermal toxicity study in minipig, a 7-day primary skin irritation study in rabbit, and a skin sensitization study in guinea pig.

In the pivotal 39-week dermal toxicity study in minipig, application of Corplex Donepezil TDS (1, 2, or 4 10 mg/day patches per animal per week) or placebo (4 patches per animal per week) resulted in skin irritation (very slight to well-defined erythema, occasionally with very slight edema) at the site of application, with increased incidence and severity observed in the donepezil group. Moderate to severe erythema was rarely observed, and no irritation was observed in recovery animals by 24 hours after removal of the final patch. Histopathology evaluation showed increases in the severity of hyperkeratosis, rete pegs, and mononuclear cell infiltration at the application sites in donepezil groups compared to placebo or untreated groups and dose-dependent increases in the incidence and severity of mononuclear cell infiltration in untreated skin sites. Minimal to mild mononuclear cell infiltration in skin of the application site remained increased in HD animals compared to placebo and untreated groups after the 6-week recovery period. Other differences observed between HD and placebo groups included increased final body weight (18% M, 5.7% F) and increased serum globulin (55% M, 42% F).

In the 7-day primary skin irritation study in rabbit, application of Corplex Donepezil TDS 10 mg/day patches cut into 25 mm x 25 mm squares resulted in a Primary Irritation score of 1.4, slightly higher than that observed in the placebo patch-treated animals (1.0). Both were considered to be slight irritants.

In the skin sensitization study in guinea pigs, no evidence of delayed dermal contact sensitization was observed in animals challenged with 6-hour applications of Corplex Donepezil TDS 10 mg/day or placebo patches cut into 25 mm x 25 mm squares, 14 days after a 3-week induction period with Corplex Donepezil TDS 10 mg/day or placebo patch squares applied for 6 hours three times per week.

As illustrated in the table below, mean $AUC_{0\text{-}168\ hr}$ values achieved in the 39-week minipig study were much lower than those observed in humans administered ADLARITY 10 mg/day patches for 4 weeks in the pivotal bioequivalence study, even using the maximum feasible dose, four 10 mg/day patches per animal per week. However, this is not a safety concern because the systemic toxicity of donepezil has already been adequately assessed in nonclinical studies supporting FDA approval of oral donepezil at doses up to 23 mg per day.

The 39-week study in minipig, together with the pivotal primary skin irritation and skin sensitization studies in rabbit and guinea pig, respectively, adequately assessed the local toxicity of Corplex Donepezil TDS.

Plasma Exposure in 39-Week Minipig Study vs. Clinical Bioequivalence Study

Toxicity	Duration, Species, Study	Dose/NOAEL	Mean $AUC_{0\text{-}168\ hr}$ (ng•hr/mL)	Exposure Margin Based on AUC
Application site skin irritation (erythema) and minimal to moderate hyperkeratosis, increased rete pegs, and mononuclear cell infiltration	39-week minipig	4 donepezil 10 mg/day TDS per animal per week	505-1800**	0.065x-0.23x
	5-week* human BE Study P-15086	1 donepezil 10 mg/day TDS per week	7798***	--

**4 weeks at one 10 mg/day TDS per week, following 1 week at one 5 mg/day TDS*

***Mean $AUC_{0\text{-}168\ hr}$ values were 608, 882, 820, and 505 ng*hr/mL in M, and 874, 1800, 1160, and 792 ng*hr/mL in F, in Weeks 1, 4, 12, and 39, respectively, from page 41 of Study Report*

****Week 5 $AUC_{0\text{-}168\ hr,\ ss}$, from page 1046 of Study Report*

Recommendations

The nonclinical data submitted adequately support the approval of ADLARITY for the treatment of patients with Alzheimer's disease.

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/s/

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07/20/2020 11:38:32 AM

LOIS M FREED
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I concur.