

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212304Orig1s000

CLINICAL REVIEW(S)

Review and Evaluation of Clinical Data

NDA	212304
Sponsor:	Corium
Product:	ADLARITY
Proposed Indication:	Alzheimer's Disease
Material Submitted:	Class 2 Resubmission
Correspondence Date:	9/11/21
Date Received By Reviewer:	9/13/21
Date Review Completed:	3/9/22
Reviewer:	Brian Trummer, M.D., Ph.D.

1. Background

This submission is a resubmission of the NDA 212304 for Adlarity (donepezil transdermal system), also known as Corplex Donepezil Transdermal system, where the sponsor responded to deficiencies and additional comments identified in the Complete Response Letter issued for this application on July 23, 2020.

This New Drug Application (NDA) was originally submitted on September 30, 2019. At the end of the initial period of review of that submission, a Complete Response was issued in a letter dated 7/23/20. The text of that Complete Response letter is included in this review, as well as the Sponsor's response on 9/11/21. Please refer to Agency reviews of that submission for further details.

Adlarity (donepezil transdermal system), also known as Corplex Donepezil Transdermal System, has been developed by the sponsor for the treatment of mild, moderate, and severe dementia of the Alzheimer's type. In response to the Complete Response letter, the sponsor has conducted three additional trials which I detail in this review on analyzing the clinical study reports.

- Clinical Study Report CL-P-20003 evaluated the steady-state pharmacokinetics of 5 mg/day and 10 mg/day Corplex Donepezil transdermal system manufactured with the commercial process compared to oral administration of 10-mg Aricept in healthy volunteers. It should be noted that this study differed from the previous manufacturing process by (b) (4)

- Clinical Study Report CL-P-20004 compared Corplex Donepezil transdermal delivery system of different ages stored at 5°C and evaluated the relative bioavailability of Corplex Donepezil transdermal delivery system, which had been maintained at refrigerated storage conditions (2 to 8°C) for at least 18 months from its date of manufacture, to Corplex Donepezil transdermal delivery system manufactured with the commercial process, which had been maintained at refrigerated storage conditions (2

to 8°C) for approximately 6 months from its date of manufacture, in healthy volunteers after single-dose applications (1-week wear).

- Clinical Study Report CL-P-19005 compared the relative bioavailability, safety, and tolerability (including local skin irritation) of Corplex™ donepezil transdermal delivery systems with crystals (crystals covering (b) (4) % within the active delivery area) with Corplex Donepezil TDS without crystals.

This review details the design and results of the three clinical studies, my assessment of this data, and my overall recommendation that based on the clinical safety data submitted in studies CL-P-20003, CL-P-20004, and CL-P-19005, I would recommend approval of Adlarity.

2. Text of Agency Complete Response Letter: July 23, 2020

The full text of the Agency Complete Response Letter has been copied verbatim into my review and is as follows:

The following 8 pages have been withheld in full as duplicate text of Complete Response letter. Please see the OtherActionsLtrs section for the letter.

The previous 8 pages have been withheld in full as duplicate text of Complete Response letter. Please see the OtherActionsLtrs section for the letter.



PROPRIETARY NAME

Please refer to correspondence dated September 19, 2019, which addresses the proposed proprietary name, ADLARITY. This name was found acceptable pending

approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug/product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, you should incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the re-tabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug/product. Include an updated estimate of use for drug/product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "RESUBMISSION" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial

response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Teresa Wheelous, Regulatory Project Manager, at teresa.wheelous@fda.hhs.gov.

3. Sponsor's Cover Letter to the Current Resubmission: September 11, 2021



4. New Clinical Data in Current Submission

4.1 Summary Description of Study CL-P-20003

4.1.1 Study Design

Clinical Study Report CL-P-20003 states that the study was conducted to evaluate the steady-state pharmacokinetics of 5 mg/day and 10 mg/day Corplex Donepezil transdermal system manufactured with the commercial process compared to oral administration of 10-mg Aricept in healthy volunteers. It should be noted that this study differed from the previous manufacturing process by

(b) (4)

4.1.1.1 Objectives

- The primary objective of the study was to evaluate the bioequivalence of steady-state donepezil plasma exposure following once-weekly treatments with 10 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM compared to once-daily oral administration of 10-mg Aricept.
- Secondary objectives included the evaluation of the bioequivalence of steady-state donepezil plasma exposure (after dose normalization) following once-weekly treatments with 5 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM compared to once-daily oral administration of 10-mg Aricept and to evaluate the adhesion to the skin during the wear period of each once-weekly 5 mg/day and 10 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM application.

- The safety objective was to evaluate the safety and tolerability, including local skin tolerability (dermal response and other effects) of once-weekly Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM.

4.1.1.2 Study Design

- This was a Phase 1, open-label, randomized, 3-period, 3-treatment, crossover study to evaluate the steady-state PK of 5 mg/day and 10 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM manufactured with the commercial process compared to 10 mg/day oral Aricept in healthy volunteers.).

4.1.1.3 Study Plan

- The study consisted of a Screening Period, a Treatment Phase with 3 treatment periods and a Follow-Up Visit. The Screening Period lasted up to 28 days prior to entering the Treatment Phase, of which eligible subjects participated in 3 treatment periods each consisting of 36 days. There was no washout between treatments.
- During Treatment Period 1, all enrolled subjects received Treatment A which was 5 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM for 5 consecutive weeks (7-day wear for each of the 5 TRANSDERMAL DELIVERY SYSTEM).
- During Treatment Periods 2 and 3, the subjects were randomized to receive either sequences of Treatments B-C or Treatments C-B. Randomization to the 2 treatment sequences was stratified by the subject's gender. Subjects received the following treatments according to the randomization schedule.
 - o Treatment B was 10 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM applied weekly (within ± 1 hour of application time on Day 37 or Day 73) for 5 consecutive weeks.
 - o Treatment C was 10-mg Aricept tablet administered once daily (within ± 1 hour of dosing time on Day 37 or Day 73) for 5 consecutive weeks.
- The plan was for the Screening Period to enroll approximately 60 subjects to complete with 48 subjects during the Treatment Phase. A total of 60 subjects were enrolled in the study; 60 subjects received Treatment A, 55 subjects received Treatment B, and 56 subjects received Treatment C. Of those enrolled, 8 subjects discontinued early from the study.
- The main inclusion criteria included healthy male or female between 18 and 55 years of age.
- The primary objective was to evaluate the bioequivalence of steady-state donepezil plasma exposure following once-weekly treatments with 10 mg/day Corplex Donepezil TDS compared to once-daily oral administration of 10-mg Aricept.
- Safety measures were to include AEs, physical examinations, vital signs, ECG parameters, safety laboratory tests, skin irritation scores, and C-

SSRS. The sponsor used a Dermal Response score, which ranged from 0 (none or no evidence of irritation) to 7 (strong reaction spreading beyond the application site, as well as an Other Effects score, which ranged from 0 (slightly glazed appearance) to 3 (glazing with fissures, film of dried serous exudate covering all or part of the TRANSDERMAL DELIVERY SYSTEM site, or small petechial erosions and/or scabs).

4.1.2 Study Results

4.1.2.1 Pharmacokinetic Results

Table 13 Plasma Donepezil PK Parameters: Week 5–PK Population

Parameter	Treatment A: 5 mg/day Donepezil TDS: Week 5 Applied Weekly, 7-day Wear				Treatment B: 10 mg/day Donepezil TDS: Week 5 Applied Weekly, 7-day Wear			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max,ss} (h)	56	72.00 (0.00-156.00)			53	84.00 (0.00-120.00)		
C _{max,ss} (ng/mL)	56	29.90	9.123	30.5	53	62.45	19.998	32.0
T _{min,ss} (h)	56	55.498	68.2591	123.0	53	67.376	72.4733	107.6
C _{min,ss} (ng/mL)	56	20.50	7.078	34.5	53	43.23	15.615	36.1
C _{avg,ss} (ng/mL)	56	25.99	8.215	31.6	53	54.16	17.691	32.7
C _{trough,ss} (ng/mL)	56	23.95	8.340	34.8	53	50.97	18.137	35.6
Day 1 AUC _{0-24,ss} (h*ng/mL)	56	559.925	181.4379	32.4	53	1184.541	394.3021	33.3
Day 2 AUC _{0-24,ss} (h*ng/mL)	56	617.301	193.2348	31.3	53	1271.333	418.2883	32.9
Day 3 AUC _{0-24,ss} (h*ng/mL)	56	662.957	210.5153	31.8	53	1351.239	444.8005	32.9
Day 4 AUC _{0-24,ss} (h*ng/mL)	56	664.833	211.2571	31.8	53	1388.065	469.0565	33.8
Day 5 AUC _{0-24,ss} (h*ng/mL)	56	643.301	206.6501	32.1	53	1369.661	453.9761	33.1
Day 6 AUC _{0-24,ss} (h*ng/mL)	56	626.263	206.1858	32.9	53	1308.149	436.5782	33.4
Day 7 AUC _{0-24,ss} (h*ng/mL)	56	591.449	203.5744	34.4	53	1226.060	408.8482	33.3
AUC _{0-168,ss} (h*ng/mL)	56	4366.030	1380.1619	31.6	53	9099.048	2972.1114	32.7
FLUCP _{ss} (%)	56	36.71	14.812	40.4	53	35.84	14.543	40.6

Parameter	Treatment A ¹ : 5 mg/day Donepezil TDS: Week 5 Applied Weekly, 7-day Wear				Treatment C: 10 mg Aricept: Week 5 QD for 35 Days			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max,ss} (h)	-	-	-	-	53	2.02 (0.00-4.05)		
C _{max,ss} (ng/mL)	56	59.80	18.245	30.5	53	70.55	19.399	27.5
T _{min,ss} (h)	-	-	-	-	53	9.831	11.7040	119.1
C _{min,ss} (ng/mL)	56	41.00	14.156	34.5	53	39.93	14.586	36.5
C _{avg,ss} (ng/mL)	56	51.98	16.431	31.6	53	50.37	15.227	30.2
C _{trough,ss} (ng/mL)	56	47.89	16.681	34.8	53	40.00	13.902	34.8
Day 1 AUC _{0-24,ss} (h*ng/mL)	56	1119.850	362.8759	32.4	-	-	-	-
Day 2 AUC _{0-24,ss} (h*ng/mL)	56	1234.603	386.4696	31.3	-	-	-	-
Day 3 AUC _{0-24,ss} (h*ng/mL)	56	1325.914	421.0307	31.8	-	-	-	-
Day 4 AUC _{0-24,ss} (h*ng/mL)	56	1329.667	422.5141	31.8	-	-	-	-
Day 5 AUC _{0-24,ss} (h*ng/mL)	56	1286.602	413.3001	32.1	-	-	-	-
Day 6 AUC _{0-24,ss} (h*ng/mL)	56	1252.527	412.3717	32.9	-	-	-	-
Day 7 AUC _{0-24,ss} (h*ng/mL)	56	1182.898	407.1488	34.4	53	1208.94	365.438	30.2
AUC _{0-168,ss} (h*ng/mL)	56	8732.059	2760.3383	31.6	53	8462.57	2558.006	30.2
FLUCP _{ss} (%)	56	36.71	14.812	40.4	53	64.94	23.664	36.4

TDS = transdermal delivery system

Note: T_{max} reported as median (range).

[1] Concentrations for Treatment A were dose-normalized to the 10 mg dose prior to analysis by multiplying concentrations by 2.

Treatment A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

Treatment B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

Treatment C (Reference): 10 mg oral Aricept® tablets, QD for 35 days in Period 2 or 3 (no dosing on Day 36 of the period

Source data: Table 14.4.5, 14.4.6, 14.4.12, 14.4.13, 14.4.14, 14.4.16, and 14.4.17

The sponsor concluded that based on maximum and total donepezil exposure at steady-state (C_{max,ss} and AUC_{0-168,ss}), 10 mg/day TRANSDERMAL DELIVERY SYSTEM applied weekly was bioequivalent to 10 mg oral Aricept tablets administered once-daily for 35 days; GMR (90% CI) were 88.65% (81.67%-96.23%) and 108.59% (100.45% 117.38%), respectively.

4.1.2.2 Safety Results

The sponsor reported that a total of 48 (80.0%) subjects experienced TEAEs during this study, 32 (53.3%) subjects during Treatment A, 30 (54.5%) subjects during Treatment B, and 32 (57.1%) subjects during Treatment C. I have copied a table from the sponsor's report that summarizes the relevant TEAE data.

**Table 18 Overall Summary of Treatment-Emergent Adverse Events (TEAEs)
(Safety Analysis Population)**

	Treatment A (N=60)	Treatment B (N=55)	Treatment C (N=56)	Overall (N=60)
Parameter	Subjects n(%)	Subjects n(%)	Subjects n(%)	Subjects n(%)
Total Number of TEAEs	32 (53.3)	30 (54.5)	32 (57.1)	48 (80.0)
TEAE	32 (53.3)	30 (54.5)	32 (57.1)	48 (80.0)
Related-TEAE	25 (41.7)	24 (43.6)	29 (51.8)	44 (73.3)
SAE	0	0	0	0
Severe TEAE	0	0	0	0
Moderate TEAE	2 (3.3)	1 (1.8)	1 (1.8)	4 (6.7)
TEAE leading to discontinuation of study product	0	0	0	0
TEAE leading to early termination	0	0	0	0

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

C (Reference): 10 mg oral Aricept® tablets, QD for 35 days in Period 2 or 3 (no dosing on Day 36 of the period)

TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event

Related TEAEs are defined as TEAEs with a missing, possible or probable relationship to study treatment.

Subjects with multiple occurrences are counted once. Adverse events are coded using MedDRA v23.1.

Percentages are based on the number of subjects in the Safety Analysis Population by treatment and overall.

Source: Table 14.3.1.1

Of interest to this study, the sponsor compared TEAEs between Treatment B and Treatment C and found the following results:

- More gastrointestinal disorders were reported during Treatment C in 30 (53.6%) subjects versus during Treatment B in 8 (14.5%) subjects.
- More general disorders and administration site conditions were reported during Treatment B in 11 (20.0%) versus during Treatment C in 7 (12.5%) subjects.
- More nervous system disorders were reported during Treatment C in 17 (30.4%) subjects versus during Treatment B in 8 (14.5%) subjects.
- The incidence of psychiatric disorders was similar between Treatment B and Treatment C, 7 (12.7%) subjects versus 6 (10.7%) subjects.
- The incidences of gastrointestinal TEAEs for 10 mg/day Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM (Treatment B) and Aricept 10 mg/day (Treatment C), respectively, were higher for Treatment C (14.5% vs. 53.6%), including for constipation (5.5% vs. 17.9%), nausea (1.8% vs. 30.4%), and diarrhea (3.6% vs. 12.5%).
- Reports of nervous system effects of dizziness (3.6% Treatment B vs. 19.6% Treatment C) and of somnolence (0% Treatment B vs. 10.7% Treatment C) also tended to be higher for Treatment C, with reports of

headache similar for the two treatments (14.5% Treatment B vs. 12.5% Treatment C).

- The observed application site pruritus (20.0% and 9.1% for Treatments A and B, respectively) was unique to Corplex Donepezil TRANSDERMAL DELIVERY SYSTEM because of its topical skin application versus for Treatment C as an oral administration of Aricept.

Table 19 Most Common TEAEs (≥5.0% Overall) by System Organ Class and Preferred Term (Safety Analysis Population)

MedDRA SOC MedDRA PT	Treatment A (N=60) Subjects n(%)	Treatment B (N=55) Subjects n(%)	Treatment C (N=56) Subjects n(%)	Overall (N=60) Subjects n(%)
At least one TEAE	32(53.3)	30(54.5)	32(57.1)	48(80.0)
Gastrointestinal disorders	15(25.0)	8(14.5)	30(53.6)	36(60.0)
Constipation	9(15.0)	3(5.5)	10(17.9)	19(31.7)
Nausea	4(6.7)	1(1.8)	17(30.4)	19(31.7)
Diarrhoea	2(3.3)	2(3.6)	7(12.5)	9(15.0)
Abdominal pain	0	3(5.5)	1(1.8)	4(6.7)
Vomiting	1(1.7)	0	3(5.4)	4(6.7)
General disorders and administration site conditions	18(30.0)	11(20.0)	7(12.5)	29(48.3)
Application site pruritus	12(20.0)	5(9.1)	0	14(23.3)
Application site dermatitis	5(8.3)	3(5.5)	1(1.8)	8(13.3)
Fatigue	2(3.3)	1(1.8)	5(8.9)	7(11.7)
Application site irritation	3(5.0)	0	0	3(5.0)
Nervous system disorders	11(18.3)	8(14.5)	17(30.4)	23(38.3)
Headache	8(13.3)	8(14.5)	7(12.5)	16(26.7)
Dizziness	3(5.0)	2(3.6)	11(19.6)	15(25.0)
Somnolence	0	0	6(10.7)	6(10.0)
Mental impairment	0	1(1.8)	2(3.6)	3(5.0)
Psychiatric disorders	10(16.7)	7(12.7)	6(10.7)	18(30.0)
Insomnia	4(6.7)	4(7.3)	0	7(11.7)
Nightmare	5(8.3)	1(1.8)	1(1.8)	6(10.0)
Abnormal dreams	1(1.7)	2(3.6)	1(1.8)	4(6.7)
Irritability	2(3.3)	0	2(3.6)	3(5.0)
Musculoskeletal and connective tissue disorders	4(6.7)	7(12.7)	6(10.7)	15(25.0)
Muscle spasms	4(6.7)	5(9.1)	5(8.9)	12(20.0)
Injury, poisoning and procedural complications	1(1.7)	2(3.6)	3(5.4)	6(10.0)
Skin abrasion	1(1.7)	0	2(3.6)	3(5.0)

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

C (Reference): 10 mg oral Aricept® tablets, QD for 35 days in Period 2 or 3 (no dosing on Day 36 of the period)

TEAE = Treatment Emergent Adverse Event; SOC = System Organ Class; PT = Preferred Term

Subjects are counted once within a system organ class and once for each unique preferred term.

Percentages are based on the number of subjects in the Safety Analysis Population by treatment period and overall.

Adverse events are coded using MedDRA v23.1.

Source: Table 14.3.1.2

The sponsor provided a summary of adverse events by severity, noting that a total of 44 (73.3%) subjects experienced TEAEs that were mild in severity; 4 (6.7%) subjects experienced 4 TEAEs that were moderate in severity; and that no subjects experienced severe TEAEs. The sponsor commented on the 4 subjects who experienced moderate TEAEs. These were as follows:

- Subject (b) (6) experienced a nightmare of moderate severity while receiving Treatment A that was deemed possibly related to study treatment, required no concomitant treatment, and resolved.

- Subject (b) (6) experienced abdominal pain of moderate severity while receiving Treatment B that was deemed unrelated to study treatment, required no concomitant treatments, and resolved.
- Subject (b) (6) experienced a headache of moderate severity while receiving Treatment A that was deemed unrelated to study treatment, required no concomitant treatment, and resolved.
- Subject (b) (6) experienced photophobia of moderate severity while receiving Treatment C that was deemed possibly related to study treatment, required no concomitant treatment, and resolved.

The sponsor noted individual subject changes in laboratory values. Specifically:

For hematology values, shifts from baseline from normal to high or low values at the end of each study period occurred in more than 2 subjects as follows:

- Shifts from normal to high in serum erythrocytes in 4/60 (7.0%) subjects during Treatment A.
- Shifts from normal to high in serum leukocytes in 3/60 (5.3%) subjects during Treatment A.
- Shifts from normal to high in lymphocytes in 4/60 (7.0%) subjects during Treatment A and 3/55 (5.7%) subjects during Treatment B.
- Shifts from normal to high in monocytes in 3/55 (5.7%) subjects during Treatment B.
- Shifts from normal to high in eosinophils in 3/60 (5.7%) subject during Treatment A.

For chemistry values, shifts from baseline from normal to high or low values at the end of each study period occurred in more than 2 subjects as follows:

- Shifts from normal to high in urea nitrogen in 3/60 (5.3%) subjects during Treatment A, in 3/55 (3.5%) subjects during Treatment B, and in 5/56 (9.4%) subjects during Treatment C.
- Shifts from normal to high in phosphate in 7/60 (12.3%) subjects during Treatment A, in 3/55 (5.7%) subjects during Treatment B, and in 4/56 (7.5%) during Treatment C.
- Shifts from normal to high in creatine kinase in 7/55 (13.2%) subjects during Treatment B and in 3/56 (5.7%) subjects during Treatment C.

For coagulation values, shifts from baseline from normal to high or low values at the end of each study period occurred in more than 2 subjects as follows:

- Shifts from normal to high in PT in 7/55 (13.2%) subjects during Treatment B and in 3/56 (5.7%) subjects during Treatment C.
- Shifts from normal to high in aPTT in 3/55 (5.7%) subjects during Treatment B and in 4/56 (7.5%) subjects during Treatment C.

For urinalysis values, shifts from baseline from normal to high or low values at the end of each study period occurred in more than 2 subjects as follows:

- Shifts from normal to high in specific gravity in 4/55 (7.5%) subjects during Treatment B and in 5/56 (9.4%) subjects during Treatment C.

The sponsor stated that none of the shifts in lab values demonstrated a clinically meaningful pattern.

The sponsor also assessed skin tolerability and the relevant findings are adapted from a table which I copy from the study report and include in this review.

Table 22 Skin Tolerability Assessments, Skin Irritation Summary (Skin Irritation Population)

Parameter	Statistic	Treatment A	Treatment B
Number of Subjects with Patches in Skin Irritation Population	N	60	55
Number (%) of subjects with a combined skin irritation score of ≥ 3 at 30 minutes post TDS removal ¹	n (%)	31 (51.7)	30 (54.5)
Number (%) of subjects with one or more combined skin irritation scores of ≥ 3 at any timepoint between 30 minutes and 72 hours post TDS removal (i.e., at 30 minutes, 24 hours, 48 hours, or 72 hours post TDS removal) ^{1, 2}	n (%)	39 (65.0)	31 (56.4)
Number of Patches in Skin Irritation Population	N	289	268
Number (%) of patches that were removed due to an unacceptable degree of irritation	n (%)	0	0

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

1 Subjects who had one or more patches with a combined irritation score of ≥ 3 at the specified timepoints post TDS removal.

2 Due to a study administration error, only the 0.5-hour assessment was done following removal of the Week 5 TDS for Treatments A and B.

Combined skin irritation score is calculated as the sum of the dermal response and other effects scores.

Patches removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from the Skin Irritation Population.

Source: Table 14.3.7.14

The sponsor noted that no subjects were discontinued early from the study due to skin irritation and no TRANSDERMAL DELIVERY SYSTEM were removed due to unacceptable skin irritation.

A breakdown of the skin tolerability assessments using Dermal Response Scores was provided for Treatment A and Treatment B.

Table 23 Skin Tolerability Assessments, Dermal Response Scores Following TDS Removal for Weeks 1-5, Summary for Treatment A (Skin Irritation Population)

Treatment A (n = 289)			Dermal Response Score							
Visit/Timepoint	Number of Patches	Statistic	0	1	2	3	4	5	6	7
0.5 h Post-Removal	289	n (%)	8 (2.8)	83 (28.7)	155 (53.6)	41 (14.2)	0	2 (0.7)	0	0
24 h Post-Removal	203	n (%)	19 (9.4)	68 (33.5)	94 (46.3)	22 (10.8)	0	0	0	0
48 h Post-Removal	229	n (%)	16 (7.0)	109 (47.6)	79 (34.5)	23 (10.0)	0	2 (0.9)	0	0
72 h Post-Removal	230	n (%)	39 (17.0)	110 (47.8)	74 (32.2)	7 (3.0)	0	0	0	0

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

C (Reference): 10 mg oral Aricept® tablets, QD for 35 days in Period 2 or 3 (no dosing on Day 36 of the period)

Patches removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from the Skin Irritation Population.

Dermal Response Scores are defined as: 0 = no evidence of irritation; 1 = minimal erythema that is barely perceptible; 2 = definite erythema that is readily visible and minimal edema, or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema, and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond the application site.

1 Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B. Source: [Table 14.3.7.11](#)

Table 24 Skin Tolerability Assessments, Dermal Response Scores Following TDS Removal for Weeks 1-5, Summary for Treatment B (Skin Irritation Population)

Treatment B (n = 268)			Dermal Response Score							
Visit/Timepoint	Number of Patches	Statistic	0	1	2	3	4	5	6	7
0.5 h Post-Removal	268	n (%)	0	51 (19.0)	173 (64.6)	43 (16.0)	0	1 (0.4)	0	0
24 h Post-Removal	214	n (%)	1 (0.5)	66 (30.8)	133 (62.1)	14 (6.5)	0	0	0	0
48 h Post-Removal	207	n (%)	21 (10.1)	64 (30.9)	115 (55.6)	7 (3.4)	0	0	0	0
72 h Post-Removal	212	n (%)	21 (9.9)	92 (43.4)	96 (45.3)	3 (1.4)	0	0	0	0

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

C (Reference): 10 mg oral Aricept® tablets, QD for 35 days in Period 2 or 3 (no dosing on Day 36 of the period)

Patches removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from the Skin Irritation Population.

Dermal Response Scores are defined as: 0 = no evidence of irritation; 1 = minimal erythema that is barely perceptible; 2 = definite erythema that is readily visible and minimal edema, or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema, and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond the application site.

1 Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B. Source: [Table 14.3.7.11](#)

A breakdown of the skin tolerability assessments using Other-Effects Scores was provided for Treatment A and Treatment B.

Table 25 Skin Tolerability Assessments, Other-Effects Scores Following TDS Removal for Weeks 1-5, Summary for Treatment A (Skin Irritation Population)

Treatment A (n =289)									
			Other-Effects Score						
Visit/Timepoint	Number of Patches	Statistic	None (0)	A (0)	B (1)	C (2)	F (3)	G (3)	H (3)
0.5 h Post-Removal	289	n (%)	0	270 (93.4)	19 (6.6)	0	0	0	0
24 h Post-Removal	203	n (%)	0	198 (97.5)	2 (1.0)	2 (1.0)	0	0	1 (0.5)
48 h Post-Removal	229	n (%)	0	210 (91.7)	13 (5.7)	6 (2.6)	0	0	0
72 h Post-Removal	230	n (%)	0	230 (100)	0	0	0	0	0

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

Patches removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from the Skin Irritation Population.

Other Effects Scores are defined as: None (0) = no other effects observed; A (0) = slightly glazed appearance;

B (1) = markedly glazed appearance; C (2) = glazing with peeling and cracking; F (3) = glazing with fissures; G (3) = film of dried serous exudate covering all or part of the TDS site; H (3) = small petechial erosions and/or scabs.

1 Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B.

Source: Table 14.3.7.12

Table 26 Skin Tolerability Assessments, Other-Effects Scores Following TDS Removal for Weeks 1-5, Summary for Treatment B (Skin Irritation Population)

Treatment B (n =268)									
			Other-Effects Score						
Visit/Timepoint	Number of Patches	Statistic	None (0)	A (0)	B (1)	C (2)	F (3)	G (3)	H (3)
0.5 h Post-Removal	268	n (%)	0	260 (97.0)	8 (3.0)	0	0	0	0
24 h Post-Removal	214	n (%)	1 (0.5)	213 (99.5)	0	0	0	0	0
48 h Post-Removal	207	n (%)	0	207 (100)	0	0	0	0	0
72 h Post-Removal	212	n (%)	0	207 (97.6)	3 (1.4)	0	0	1 (0.5)	1 (0.5)

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

Patches removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from the Skin Irritation Population.

Other Effects Scores are defined as: None (0) = no other effects observed; A (0) = slightly glazed appearance;

B (1) = markedly glazed appearance; C (2) = glazing with peeling and cracking; F (3) = glazing with fissures; G (3) = film of dried serous exudate covering all or part of the TDS site; H (3) = small petechial erosions and/or scabs.

1 Due to a study administration error, only the 0.5-hour assessment was performed following removal of the Week 5 TDS for Treatments A and B.

Source: Table 14.3.7.12

As adhesion was a concern for the patches, the sponsor provided adhesion assessments of the patches as provided in the following sponsor provided table.

Table 27 Adhesion Assessments, Patch Adhesion Summary Data (Adhesion Population) Weeks 1-5 Summary

Week	Parameter	Statistic	Treatment A (N=293)	Treatment B (N=270)
Weeks 1-5	Mean Adhesion Score ¹	n	293	270
		Mean (SD)	92.59 (10.881)	93.30 (8.802)
		Median (Q1, Q3)	95.93 (91.43, 98.43)	96.25 (91.36, 98.86)
		Min, Max	9.3, 100.0	41.4, 100.0
	Number (%) of patches with complete detachment during the 7-day wear period	n (%)	4 (1.4)	2 (0.7)
	Number (%) of patches with adhesion <50% at any adhesion measurement timepoint during the 7-day wear period	n (%)	15 (5.1)	9 (3.3)
Weeks 1-5	Time (hour) post TDS application patch was first observed with adhesion <50% during the 7-day wear period	n	15	9
		Mean (SD)	121.5 (34.45)	108.1 (35.87)
		Median (Q1, Q3)	120.1 (95.7, 155.9)	107.9 (83.9, 132.8)
		Min, Max	36, 167	48, 157
	Number (%) of patches with adhesion ≥75% at all adhesion assessment timepoints during the 7-day wear period	n (%)	245 (83.6)	232 (85.9)

A (Test): 5 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 1 Day 36

B (Test): 10 mg/day TDS applied weekly, 7-day wear, removed in the morning of Period 2 or 3 Day 36

¹The mean adhesion score is the average of the adjusted adhesion percentages from 12 hours post-application to 168 hours post-application. The adjusted adhesion percentage at a post-application timepoint for a given TDS

is the lowest post-application score observed at or prior to the timepoint. If a patch became completely detached before the end of 7-day wear period (Hour 168), a 0% adhered score was carried forward for all subsequent patch assessments.

Source: Table 14.3.7.19

The sponsor noted that there were no serious adverse events or deaths reported for subjects during this study.

4.2 Summary Description of Study CL-P-2004

4.2.1 Study Design

Clinical Study Report CL-P-20004 states that the study was conducted to compare Corplex Donepezil TDS of different ages stored at 5°C, the present study evaluated the relative bioavailability of Corplex Donepezil TDS, which had been maintained at refrigerated storage conditions (2 to 8°C) for at least 18 months from its date of manufacture, to Corplex Donepezil TDS manufactured with the commercial process, which had been maintained at refrigerated storage conditions (2 to 8°C) for approximately 6 months from its date of manufacture, in healthy volunteers after single-dose TDS applications (1-week wear). Since an adequate number of 5 mg/day Corplex Donepezil TDS stored at 5°C for at least 18 months were available to conduct the present study, a 5 mg/day dose for both young and older patches in the study was utilized instead of TDS with the higher intended clinical dose of 10 mg/day.

- The primary objective of the study was to compare the PK parameters of Corplex Donepezil TDS of different ages.
- Secondary objectives included the evaluation of the safety, skin tolerability (Dermal Response and Other Effects), and adhesion of Corplex Donepezil TDS of different ages.
- This was a Phase 1, open-label, randomized, 2-period, 2-treatment, crossover PK study comparing a Corplex Donepezil TDS that had been maintained at refrigerated storage conditions (2 to 8°C) for at least 18 months from its date of manufacture to a Corplex Donepezil TDS manufactured with the commercial process maintained at refrigerated storage conditions (2 to 8°C) for approximately 6 months from its date of manufacture in healthy volunteers.
- The study consisted of Screening Period (up to 28 days prior to entering the Treatment Phase), a Treatment Phase with 2 Treatment Periods (each consisting of 7 days separated by a washout of 28 days), and a Follow-up Phone Call. The treatment phases (randomized to receive either sequence Treatments A-B or Treatments B-A) consisted of:
 - o Treatment A (Test): 5 mg/day Corplex Donepezil TDS, which had been maintained at refrigerated storage conditions (2 to 8°C) for at least 18 months from its date of manufacture.
 - o Treatment B (Reference): 5 mg/day Corplex Donepezil TDS manufactured with the commercial process, which had been maintained at refrigerated storage conditions (2 to 8°C) for approximately 6 months from its date of manufacture.
- A total number of approximately 54 patients would be enrolled to complete with approximately 42 subjects.
- The main inclusion criteria were being a healthy male or female between 18 and 55 years of age.
- The primary efficacy parameter was pharmacokinetic variables that included drug concentration measurements.
- Safety measures were to include adverse events, laboratory evaluations including total hematology, serum chemistry, urinalysis, vital signs, physical examinations, ECGs, Columbia-Suicide Severity rating scale, dermal response scores and other-effects scores.

4.2.2 Study Results

The sponsor provided a table regarding the pharmacokinetic data comparing 5 mg/day patches stored in refrigerated conditions for at least 18 months (Treatment A) compared to those stored in refrigerated conditions for approximately 6 months (Treatment B)

Table 10 Plasma Donepezil PK Parameters (Primary PK Analysis) – Primary PK Population

Parameter	Treatment A: 5 mg/day Donepezil TDS Maintained for 24 Months				Treatment B: 5 mg/day Donepezil TDS Maintained for 5 Months			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{lag} (h)	49	11.918	7.9263	66.5	50	10.120	6.4068	63.3
T _{max} (h) ^a	49	167.92 (108.00-180.00)			50	156.00 (108.00-178.00)		
C _{max} (ng/mL)	49	13.59	5.593	41.2	50	14.75	5.761	39.0
T _{last} (h)	49	562.776	68.4213	12.2	50	562.560	62.6894	11.1
C _{last} (ng/mL)	49	0.63	0.400	64.0	50	0.62	0.346	55.7
AUC ₀₋₁₆₈ (h*ng/mL)	49	1306.362	642.6273	49.2	50	1444.151	639.0821	44.3
AUC _{0-last} (h*ng/mL)	49	2694.800	1269.9484	47.1	50	2956.895	1295.9676	43.8
AUC _{0-inf} (h*ng/mL)	49	2783.924	1321.2113	47.5	50	3043.923	1339.2958	44.0
AUC _{extrap} (%)	49	3.33	2.343	70.4	50	2.99	1.86	62.3
T _{1/2} (h)	49	91.848	25.4120	27.7	50	91.238	23.8521	26.1

TDS = transdermal delivery system

^a T_{max} reported as median (range)

Treatment A (Test) = 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) for approximately 24 months from its date of manufacture (n=49)

Treatment B (Reference) = 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture (n=50)

Primary PK Analysis = Subjects (b) (6), and (b) (6) were excluded from Treatment A and Subjects (b) (6), and (b) (6) were excluded from Treatment B

Source: Table 14.4.3

There were only 6 treatment emergent adverse events, all of which occurred in Treatment A. They each occurred in 1 subject, and included conjunctival hyperemia, chills, nasopharyngitis, muscle spasms, anxiety, and cough. The data from these TEAEs are provided in the table copied from the sponsor's submission.

Table 16 Overall Summary of Treatment-Emergent Adverse Events (TEAEs) (Safety Analysis Population)

	Treatment A ¹ (N=54)	Treatment B ² (N=52)	Overall (N=54)
Parameter	Subjects n(%)	Subjects n(%)	Subjects n(%)
Total Number of TEAEs	6 (11.1)	0	6 (11.1)
TEAE	6 (11.1)	0	6 (11.1)
Related-TEAE	2 (3.7)	0	2 (3.7)
SAE	0	0	0
Severe TEAE	0	0	0
Moderate TEAE	2 (3.7)	0	2 (3.7)
TEAE leading to discontinuation of study product	2 (3.7)	0	2 (3.7)
TEAE leading to early termination	2 (3.7)	0	2 (3.7)

1 A (Test): 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) for approximately 24 months from its date of manufacture

2 B (Ref.): 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture

TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event

Subjects with multiple occurrences are counted once.

Percentages are based on the number of subjects in the Safety Analysis Population by treatment and overall.

Adverse events are coded using MedDRA v23.1.

Source: [Table 14.3.1.1](#)

A full accounting of the 6 treatment emergent adverse events is provided in Table 17 copied from the sponsor's submission.

Table 17 Number (%) of Subjects with TEAEs by System Organ Class and Preferred Term (Safety Analysis Population)

MedDRA SOC MedDRA PT	Treatment A ¹ (N=54) Subjects n(%)	Treatment B ² (N=52) Subjects n(%)	Overall (N=54) Subjects n(%)
At least one TEAE	6 (11.1)	0	6 (11.1)
Eye disorders	1 (1.9)	0	1 (1.9)
Conjunctival hyperaemia	1 (1.9)	0	1 (1.9)
General disorders and administration site conditions	1 (1.9)	0	1 (1.9)
Chills	1 (1.9)	0	1 (1.9)
Infections and infestations	1 (1.9)	0	1 (1.9)
Nasopharyngitis	1 (1.9)	0	1 (1.9)
Musculoskeletal and connective tissue disorders	1 (1.9)	0	1 (1.9)
Muscle spasms	1 (1.9)	0	1 (1.9)
Psychiatric disorders	1 (1.9)	0	1 (1.9)
Anxiety	1 (1.9)	0	1 (1.9)
Respiratory, thoracic and mediastinal disorders	1 (1.9)	0	1 (1.9)
Cough	1 (1.9)	0	1 (1.9)

1 A (Test): 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) for approximately 24 months from its date of manufacture

2 B (Ref.): 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture

TEAE = Treatment Emergent Adverse Event; SOC = System Organ Class; PT = Preferred Term

Subjects are counted once within a system organ class and once for each unique preferred term.

Percentages are based on the number of subjects in the Safety Analysis Population by treatment and overall.

Adverse events are coded using MedDRA v23.1.

Source: [Table 14.3.1.2](#)

It should be noted that the two treatment emergent adverse events deemed related to study treatment included chills and muscle spasms. The two treatment emergent adverse events that resulted in discontinuation of the subjects from the study product and early termination for the subjects from the study included muscle spasms and anxiety. Four of the six TEAEs were mild in severity with the two exceptions being nasopharyngitis and muscle spasms which were moderate.

As the muscle spasms were both moderate in severity and classified as related to study treatment and led to treatment discontinuation, I discuss the details here. This involved a 27 year old hispanic male with bilateral lower extremity cramps after receiving a 5 mg/day patch refrigerated for at least 18 months from manufacture date. This was reported on study day 1 and the subject received Pedialyte that day and had the patch removed on study day 2.

The sponsor, while noting shifts from baseline in lab values, found that none of the shifts in hematology, serum chemistry, coagulation, or urinalysis parameters were considered by the Investigator to be clinically significant. Similarly, changes in vital signs and ECGs were not meaningful.

Skin assessments were taken for this study as well.

Table 19 Skin Tolerability Assessments, Skin Irritation Summary (Skin Irritation Population)

Parameter	Statistic	Treatment A ¹ (N=49)	Treatment B ² (N=50)
Number (%) of subjects with a combined skin irritation score of ≥ 3 at 30 minutes post TDS removal	n (%)	7 (14.3)	7 (14.0)
Number (%) of subjects with one or more combined skin irritation scores of ≥ 3 at any time point between 30 minutes and 72 hours post TDS removal (i.e., at 30 minutes, 24 hours, 48 hours, or 72 hours post TDS removal)	n (%)	9 (18.4)	7 (14.0)
Number (%) of patches that were removed due to an unacceptable degree of irritation	n (%)	0	0

1. A (Test): 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) approximately 24 months from its date of manufacture

2. B (Ref.): 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture

Source: Table 14.3.7.14

Table 20 Skin Tolerability Assessments, Dermal Response Scores (Skin Irritation Population)

Treatment A ¹ (N =49)		Dermal Response Score							
Visit/Time Point	Statistic	0	1	2	3	4	5	6	7
Day 1, Pre-Application	n (%)	49 (100)	0	0	0	0	0	0	0
0.5 h Post-Removal	n (%)	7 (14.3)	32 (65.3)	9 (18.4)	0	0	1 (2.0)	0	0
24 h Post-Removal	n (%)	23 (46.9)	22 (44.9)	4 (8.2)	0	0	0	0	0
48 h Post-Removal	n (%)	32 (65.3)	16 (32.7)	1 (2.0)	0	0	0	0	0
72 h Post-Removal	n (%)	40 (81.6)	8 (16.3)	1 (2.0)	0	0	0	0	0
Treatment B ² (N =50)		Dermal Response Score							
Visit/Time Point	Statistic	0	1	2	3	4	5	6	7
Day 1, Pre-Application	n (%)	50 (100)	0	0	0	0	0	0	0
0.5 h Post-Removal	n (%)	5 (10.0)	35 (70.0)	10 (20.0)	0	0	0	0	0
24 h Post-Removal	n (%)	19 (38.0)	27 (54.0)	4 (8.0)	0	0	0	0	0
48 h Post-Removal	n (%)	34 (68.0)	15 (30.0)	1 (2.0)	0	0	0	0	0
72 h Post-Removal	n (%)	39 (78.0)	7 (14.0)	4 (8.0)	0	0	0	0	0

1. A (Test): 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) approximately 24 months from its date of manufacture

2. B (Ref.): 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture

Dermal Response Scores are defined as: 0 = No evidence of irritation; 1 = Minimal erythema that is barely perceptible; 2 = Definite erythema that is readily visible and minimal edema or minimal papular response; 3 = Erythema and papules; 4 = Definite edema; 5 = Erythema, edema, and papules; 6 = Vesicular eruption; 7 = Strong reaction spreading beyond the application site

N = Number of TDS in the Skin Irritation Population

If a patch was removed due to excessive irritation, dermal response scores were imputed at scheduled assessments after patch removal using last available observation carried forward.

Source: Table 14.3.7.11

Table 21 Skin Tolerability Assessments, Other-Effects Scores (Skin Irritation Population)

Treatment A ¹ (N=49)		Other Effects Score						
Visit/Time Point	Statistic	None (0)	A (0)	B (1)	C (2)	F (3)	G (3)	H (3)
Day 1, Pre-Application	n (%)	49 (100)	0	0	0	0	0	0
0.5 h Post-Removal	n (%)	42 (85.7)	1 (2.0)	0	0	0	0	6 (12.2)
24 h Post-Removal	n (%)	46 (93.9)	0	0	0	0	0	3 (6.1)
48 h Post-Removal	n (%)	46 (93.9)	0	0	0	0	0	3 (6.1)
72 h Post-Removal	n (%)	48 (98.0)	0	0	0	0	0	1 (2.0)
Treatment B ² (N=50)		Other Effects Score						
Visit/Time Point	Statistic	None (0)	A (0)	B (1)	C (2)	F (3)	G (3)	H (3)
Day 1, Pre-Application	n (%)	50 (100)	0	0	0	0	0	0
0.5 h Post-Removal	n (%)	42 (84.0)	1 (2.0)	0	0	0	0	7 (14.0)
24 h Post-Removal	n (%)	46 (92.0)	0	0	0	0	0	4 (8.0)
48 h Post-Removal	n (%)	49 (98.0)	0	0	0	0	0	1 (2.0)
72 h Post-Removal	n (%)	49 (98.0)	0	0	0	0	0	1 (2.0)

1. A (Test): 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) approximately 24 months from its date of manufacture

2. B (Ref.): 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture

Other Effects Scores are defined as: None (0) = No other effects observed; A (0) = Slightly glazed appearance;

B (1) = Markedly glazed appearance; C (2) = Glazing with peeling and cracking; F (3) = Glazing with fissures;

G (3) = Film of dried serous exudate covering all or part of the TDS site; H (3) = Small petechial erosions and/or

scabs Source: [Table 14.3.7.12](#)

As adhesion was a concern leading to the resubmission, the sponsor compared adhesion characteristics of Treatment A and Treatment B.

Table 22 Adhesion Assessments, Patch Adhesion Summary Data (Adhesion Population)

Parameter	Statistic	Treatment A ¹ (N=53)	Treatment B ² (N=52)
Mean Adhesion Score ³	n	53	52
	Mean (SD)	90.81 (13.286)	93.10 (9.414)
	Median (Q1, Q3)	96.13 (90.47, 98.00)	96.10 (92.50, 98.57)
	Min, Max	31.6, 100.0	54.6, 100.0
Number (%) of patches with complete detachment during the 7-day wear period	n (%)	4 (7.5)	2 (3.8)
Number (%) of patches with adhesion <50% at any adhesion measurement time point during the 7-day wear period	n (%)	5 (9.4)	3 (5.8)
Time (hour) post TDS application patch was first observed with adhesion <50% during the 7-day wear period	n	5	3
	Mean (SD)	110.4 (26.02)	120.0 (24.00)
	Median (Q1, Q3)	108.1 (108.0, 120.0)	120.1 (96.0, 144.0)
	Min, Max	72, 144	96, 144
Number (%) of patches with adhesion ≥75% at all adhesion assessment time points during the 7-day wear period	n (%)	40 (75.5)	45 (86.5)

1. A (Test): 5 mg/day donepezil TDS, which has been maintained at refrigerated storage conditions (2-8°C) approximately 24 months from its date of manufacture
2. B (Ref.): B (Ref.): 5 mg/day donepezil TDS, manufactured with the commercial process which has been maintained at refrigerated storage conditions (2-8°C) for approximately 5 months from its date of manufacture
3. The mean adhesion score is the average of the adjusted adhesion percentages from 12 hours post-application to 168 hours post-application. The adjusted adhesion percentage at a post-application time point for a given TDS is the lowest post-application score observed at or prior to the time point. If a patch became completely detached before the end of 7-day wear period (Hour 168), a 0% adhered score was carried forward for all subsequent patch assessments.

Source: Table 14.3.7.19

There were no deaths or other serious adverse events reported during the study.

4.3 Summary Description of Study CL-P-19005

4.3.1 Study Design

Clinical Study Report CL-P-19005 describes a Phase 1, randomized, blinded, 2-way crossover study to assess the relative bioavailability of Corplex™ donepezil transdermal delivery systems with and without crystals.

- The primary objective of the study was to assess relative bioavailability of donepezil from single application of once-weekly Corplex™ Donepezil Transdermal Delivery Systems (TDS) with crystals (crystals covering (b) (4) % within the active delivery area) compared to Corplex Donepezil TDS without crystals.
- The secondary objectives were to evaluate the safety and tolerability (including local skin irritation) of Corplex Donepezil TDS.

- This was a Phase 1, randomized, blinded, 2-way crossover study to assess the relative bioavailability of Corplex™ donepezil transdermal delivery systems with and without crystals.
- The study design consisted of subjects being randomized to 1 of 4 treatment sequences. In the first treatment period, each subject received a single application of once-weekly Donepezil TDS (with crystals or with no crystals), applied to either the left or right side of the back according to his or her randomization. After a washout period of 49 days, the subject had the other Donepezil TDS type applied by blinded site staff on the opposite side of the back during Treatment Period 2. In Treatment Period 1, 24 subjects received Donepezil TDS with crystals treatment (12 applied to the left and 12 applied to the right side of back), and 24 subjects received Donepezil TDS with no crystals treatment (12 applied to the left and 12 applied to the right side of back). Subjects who completed Period 1 received the other TDS treatment in Period 2.
- A total number of 48 healthy male and female volunteers ≥ 18 years of age were studied. Forty-eight subjects were treated during Treatment Period 1 and 42 subjects were treated during Treatment Period 2. The Safety Population for each treatment included all subjects that received study drug. Across both study periods, 46 subjects received Donepezil TDS with crystals and 44 subjects received Donepezil TDS no crystals.
- The duration of treatment consisted of exposure to donepezil for up to 7 consecutive days. Study duration was approximately 133 days from screening to final study procedures and included: A screening period of up to 6 weeks (42 days); Treatment Period 1: 7 days Donepezil TDS wear + 49 days washout (56 days); and Treatment Period 2: 7 days Donepezil TDS wear + 28 days post wear follow-up (35 days).
- The main inclusion criteria were healthy, adult, male or female, ≥ 18 years of age at screening, had a body mass index ≥ 18.0 and ≤ 32.0 kg/m² at screening, were medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or electrocardiograms (ECGs), as deemed by the Principal Investigator, and had a Fitzpatrick skin type of I, II, or III or skin colorimeter scores equivalent to the allowed Fitzpatrick skin type.
- The pharmacokinetic variables studied plasma donepezil concentrations included area under the plasma concentration-time curve during a 1-week application time from 0 to 168 hours (AUC₀₋₁₆₈), AUC up to the time of last measurable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{inf}), AUC extrapolated from time t to infinity as a percentage of AUC_{inf} (%AUC_{extrap}), maximum observed plasma concentration (C_{max}), observed time of C_{max} (T_{max}), lag time for absorption (T_{lag}), apparent first-order terminal elimination half-life (T_{1/2}), and elimination rate constant (K_{el}). Relative bioavailability of Donepezil TDS with crystals compared to Donepezil TDS with no crystals was assessed based on the PK endpoints. Bioequivalence (BE) of C_{max} and AUC_{inf} was used to determine the comparability of the 2 treatments.

- The adhesion variables assessed at 12-hour intervals throughout the patch wear period using adhesion scales based on the adhered area (%) for each patch.
- Safety variables studied for safety and skin tolerability evaluations included: adverse event (AE) monitoring, clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis), vital signs, physical examinations, ECGs, skin irritation assessments (graded using dermal response and other effects scales), and suicidality monitoring as per the Columbia-Suicide Severity Rating Scale (C-SSRS).

4.3.2 Study Results

4.3.2.1 Pharmacokinetic Results

The sponsor states the following pharmacokinetic conclusions from the study in their synopsis of study CL-P-19005:

- Plasma donepezil concentration profiles were similar for Donepezil TDS with crystals and Donepezil TDS with no crystals.
- Individual and mean donepezil PK parameters were similar between treatments in terms of parameters characterizing absorption (T_{lag} , T_{max} and C_{max}), exposure (AUC_{inf} and AUC_{0-168}), and elimination ($T_{1/2}$). This indicated that the presence of crystals in the TDS (at the levels used in this study) would not be expected to change the pharmacokinetics of donepezil.
- Point estimates for the ratios of Donepezil TDS with crystals and Donepezil TDS with no crystals for AUC_{inf} and C_{max} were 0.94 and 0.93, respectively, indicating a similar exposure to donepezil after each treatment. The 2 treatments were bioequivalent (ie, the 90% confidence intervals for both AUC_{inf} and C_{max} fell within the acceptance range for bioequivalence of 0.80 to 1.25).

These conclusions arise from data tables provided in the clinical study report for protocol CL-P-19005.

Table 12: Summary of Mean (CV%) PK Parameters by Treatment (Study CL-P-19005, PK Population)

Treatment	T _{lag} (h)	T _{max} (h)	C _{max} (ng/mL)	AUC ₀₋₁₆₈ (h·ng/mL)	AUC _{0-t} (h·ng/mL)	AUC _{inf} (h·ng/mL)	%AUC _{extrap}	K _{el} (h ⁻¹)	T _{1/2} (h)
Donepezil TDS Crystals (n = 45)	21.212 (50.3%)	157.668 (12.7%)	18.30 (45.9%)	1779.124 (51.8%)	3809.486 (45.2%)	3869.913 (44.4%)	1.95 (65.8%)	0.00766 (27.7%)	96.916 (26.0%)
Donepezil TDS No Crystals (n = 43)	21.648 (45.0%)	162.091 (11.1%)	18.85 (41.3%)	1828.212 (48.1%)	3932.674 (40.0%)	3988.494 (39.5%)	1.64 (61.9%)	0.00754 (29.3%)	99.106 (27.0%)

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = maximum observed plasma concentration; CV% = coefficient of variation expressed as a percentage; Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; h = hours; K_{el} = elimination rate constant; PK = pharmacokinetic; T_{1/2} = apparent first-order terminal elimination half-life; TDS = Transdermal Delivery System; T_{lag} = lag time for absorption; T_{max} = observed time of maximum observed plasma concentration.

Source: Section 14.2.1.3.

Table 13: Bioequivalence of PK Parameters (Study CL-P-19005; BE Population)

Treatment	n	Adjusted Geometric Mean ^a	Comparison	Adjusted GMR	90% CI ^{b,c}
AUC_{inf} (ng•h/mL)					
Donepezil TDS Crystals	40	3498.182	Crystals/No Crystals	0.94	0.88, 1.00
Donepezil TDS No Crystals	40	3732.314			
C_{max} (ng/mL)					
Donepezil TDS Crystals	40	16.35	Crystals/No Crystals	0.93	0.87, 0.99
Donepezil TDS No Crystals	40	17.6			

Abbreviations: AUC = area under the curve; BE = bioequivalence; CI = confidence interval; C_{max} = maximum concentration; Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; h = hour; GMR = geometric mean ratio; PK = pharmacokinetic; TDS = transdermal delivery system.

a. Adjusted geometric mean and adjusted GMR were obtained from a linear mixed-model with the natural logarithm of the PK endpoint as the response variable and sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect.

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

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

Source: Section 14.2.1.4.

4.3.2.2 Adhesion Results

The sponsor states the following adhesion conclusions from the study in their synopsis of study CL-P-19005:

- In the first 24 hours, whole patch adhesion was slightly better in the Donepezil TDS with crystals treatment (adhesion score 0: 84.1% and 54.3% at 12 and 24 hours, respectively) compared with Donepezil TDS with no crystals (67.4% and 47.7% at 12 and 24 hours, respectively). After 24 hours, whole patch adhesion was similar between treatments.
- In the first 72 hours, active area patch adhesion was slightly better in the Donepezil TDS with crystals treatment (adhesion score 0 range: 71.7% to 97.7%) compared with Donepezil TDS with no crystals (range: 63.6% to

81.4%). After 72 hours, active area patch adhesion was similar between treatments.

- No patches became 100% detached (score of 11) during any wear period, and no subjects had < 50% adhesion.
- Adhesion of the drug delivery area was greater than that of the whole patch (ie, adhesion scores tended to be lower), indicating that when patch lift occurred it tended to occur first along the inactive overlay patch border.

These conclusions arise from data in the following table provided in the clinical study report for protocol CL-P-19005.

Table 15: Adjusted Adhesion Score Frequency Summary for the Whole Patch – (Study CL-P-19005, Adhesion Population)

Treatment	n	Hours Post Patch Application	Adjusted Adhesion Score ^a									
			0	1	2	3	4	5	6	7	8	≥ 9
Donepezil TDS Crystals (N=46)	44	12 Hrs	37 (84.1%)	5 (11.4%)	2 (4.5%)	0	0	0	0	0	0	0
	46	24 Hrs	25 (54.3%)	18 (39.1%)	2 (4.3%)	0	1 (2.2%)	0	0	0	0	0
	46	36 Hrs	20 (43.5%)	23 (50.0%)	2 (4.3%)	0	1 (2.2%)	0	0	0	0	0
	46	48 Hrs	17 (37.0%)	26 (56.5%)	2 (4.3%)	0	1 (2.2%)	0	0	0	0	0
	46	60 Hrs	16 (34.8%)	26 (56.5%)	3 (6.5%)	0	1 (2.2%)	0	0	0	0	0
	46	72 Hrs	14 (30.4%)	28 (60.9%)	3 (6.5%)	0	1 (2.2%)	0	0	0	0	0
	46	84 Hrs	13 (28.3%)	29 (63.0%)	3 (6.5%)	0	1 (2.2%)	0	0	0	0	0
	46	96 Hrs	12 (26.1%)	29 (63.0%)	4 (8.7%)	0	1 (2.2%)	0	0	0	0	0
	46	108 Hrs	12 (26.1%)	29 (63.0%)	4 (8.7%)	0	1 (2.2%)	0	0	0	0	0
	46	120 Hrs	10 (21.7%)	31 (67.4%)	4 (8.7%)	0	1 (2.2%)	0	0	0	0	0
	46	132 Hrs	10 (21.7%)	31 (67.4%)	4 (8.7%)	0	1 (2.2%)	0	0	0	0	0
	46	144 Hrs	7 (15.2%)	34 (73.9%)	4 (8.7%)	0	1 (2.2%)	0	0	0	0	0
	46	156 Hrs	7 (15.2%)	33 (71.7%)	5 (10.9%)	0	1 (2.2%)	0	0	0	0	0
	46	168 Hrs	5 (10.9%)	35 (76.1%)	5 (10.9%)	0	1 (2.2%)	0	0	0	0	0
Donepezil TDS No Crystals (N=44)	43	12 Hrs	29 (67.4%)	11 (25.6%)	3 (7.0%)	0	0	0	0	0	0	0
	44	24 Hrs	21 (47.7%)	20 (45.5%)	3 (6.8%)	0	0	0	0	0	0	0
	44	36 Hrs	21 (47.7%)	20 (45.5%)	3 (6.8%)	0	0	0	0	0	0	0
	44	48 Hrs	19 (43.2%)	21 (47.7%)	3 (6.8%)	1 (2.3%)	0	0	0	0	0	0
	44	60 Hrs	15 (34.1%)	24 (54.5%)	3 (6.8%)	2 (4.5%)	0	0	0	0	0	0
	44	72 Hrs	14 (31.8%)	25 (56.8%)	3 (6.8%)	2 (4.5%)	0	0	0	0	0	0
	44	84 Hrs	13 (29.5%)	26 (59.1%)	3 (6.8%)	2 (4.5%)	0	0	0	0	0	0
	44	96 Hrs	13 (29.5%)	26 (59.1%)	3 (6.8%)	2 (4.5%)	0	0	0	0	0	0
	44	108 Hrs	11 (25.0%)	27 (61.4%)	4 (9.1%)	2 (4.5%)	0	0	0	0	0	0
	44	120 Hrs	8 (18.2%)	30 (68.2%)	4 (9.1%)	2 (4.5%)	0	0	0	0	0	0
	44	132 Hrs	8 (18.2%)	30 (68.2%)	4 (9.1%)	2 (4.5%)	0	0	0	0	0	0
	44	144 Hrs	4 (9.1%)	34 (77.3%)	4 (9.1%)	2 (4.5%)	0	0	0	0	0	0
	44	156 Hrs	3 (6.8%)	35 (79.5%)	4 (9.1%)	2 (4.5%)	0	0	0	0	0	0
	44	168 Hrs	3 (6.8%)	34 (77.3%)	5 (11.4%)	2 (4.5%)	0	0	0	0	0	0

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; TDS = transdermal delivery system.

Notes:

- Subjects whose patches were removed early for reasons unrelated to adhesion were excluded from visits following patch removal or detachment.
 - Adhesion Assessment Scores were defined as: 0 = 100%; 1 = 90% to < 100%; 2 = 80% to < 90%; 3 = 70% to < 80%; 4 = 60% to < 70%; 5 = 50% to < 60%; 6 = 40% to < 50%; 7 = 30% to < 40%; 8 = 20% to < 30%; 9 = 10% to < 20%; 10 = > 0% to < 10%; 11 = Detached.
- a. The adjusted adhesion score at a given application time point for a given TDS was the highest post-application score observed at or prior to the time point. If a patch became completely detached before the end of the 7-day wear period (Hour 168), a score of 11 was carried forward for all subsequent patch assessments.
- Source: Section 14.3.5.8.2.

4.3.2.3 Safety Results

The sponsor states the following safety conclusions from the study in their synopsis of study CL-P-19005:

- A 1-week application of Donepezil TDS with crystals (crystals covering (b) (4)% of within the active delivery area) and a 1-week application of Donepezil TDS with no crystals were safe and generally well-tolerated in healthy subjects.
- Overall, there was no clinically meaningful difference in the AE profile between Donepezil TDS with crystals and Donepezil TDS with no crystals.

The incidence of TEAEs was similar in the Donepezil TDS with crystals (78.3%) and Donepezil TDS with no crystals (70.5%) treatments. Incidences of headache (26.1%), hypertension (6.5%), and application site papules (6.5%) were higher in the Donepezil TDS with crystals treatment compared with Donepezil TDS with no crystals treatment (18.2%, 0, and 0, respectively). The incidences of treatment-related TEAEs were similar between treatments and the incidences of SAEs and TEAEs leading to discontinuation were low and similar between treatments (range: 2.2% to 4.5%); there were no deaths.

- One subject reported 2 severe TEAEs of palpitation and dizziness, which were serious and considered not related to study drug by the principal investigator; the subject discontinued study drug and the events resolved.
- The most frequently reported TEAEs ($\geq 5\%$) were abnormal dreams (37.5%), headache (31.3%), application site pruritus (20.8%), diarrhea (16.7%), nausea (14.6%), back pain (12.5%), dizziness (8.3%), and hypertension and application site papules (6.3% each). In addition to headache, hypertension, and application site papules, which had higher incidences in the Donepezil TDS with crystals treatment as noted above, back pain had a higher incidence in the Donepezil TDS with no crystals treatment (11.4%) compared with Donepezil TDS with crystals (2.2%). The other most frequently reported TEAEs were reported similarly between treatments.
- One subject in the Donepezil TDS with crystals treatment reported 2 SAEs (atrial fibrillation and troponin I increased) and 2 subjects in the Donepezil TDS with no crystals treatment reported 3 SAEs (palpitations and dizziness by 1 subject, and foot fracture by 1 subject). The SAEs of atrial fibrillation, troponin I increased, palpitations, and dizziness led to discontinuation of study drug. In addition, 1 subject receiving Donepezil TDS with crystals discontinued from the study due to a TEAE of eczema. None of the events were considered to be related to study drug by the PI and the subjects all recovered, recovered with sequelae, or were recovering.
- The most frequently reported TEAE associated with TDS application site was application site pruritus (15.2% in Donepezil TDS with crystals treatment and 11.4% in Donepezil TDS with no crystals treatment). The incidences of other TEAEs associated with TDS application site were low. All of the TEAEs associated with TDS application site were mild in severity and were considered related to study drug by the PI.
- While there were sporadic abnormalities in laboratory, ECG, and vital sign measurements, no meaningful trends were identified in these measurements with either of the 2 study treatments. In addition the C-SSRS showed no suicidal ideation and no suicidal behaviors in the subjects' responses after screening.
- The Donepezil TDS, both with crystals and with no crystals, was generally well-tolerated with little skin irritation observed for the majority of subjects

- after the first 30 minutes post removal. Any observed effects were minor to mild skin irritation (erythema), which was transient and self-resolving.
- In the Donepezil TDS with crystals treatment, a total of 6 subjects (13.0%) had combined irritation scores of ≥ 3 (erythema and papules) at any time point between 30 minutes and 72 hours; all were at 30 minutes post removal. In the Donepezil TDS with crystals treatment, a total of 5 subjects (11.4%) had combined irritation scores of ≥ 3 at any time point between 30 minutes and 72 hours; all combined irritation scores were < 3 by 72 hours. No patches were removed due to an unacceptable degree of irritation.

These conclusions arise from data tables provided in the clinical study report for protocol CL-P-19005 that I have copied and include here.

Table 16: Overall Summary of Treatment-Emergent Adverse Events (Study CL-P-19005, Safety Population)

Category	Donepezil TDS Crystals (N = 46)	Donepezil TDS No Crystals (N = 44)	All Subjects (N = 48)
	n (%)	n (%)	n (%)
All TEAEs	36 (78.3%)	31 (70.5%)	42 (87.5%)
Total number of TEAEs	99	81	180
Severe ^a	0	1 (2.3%)	1 (2.1%)
Treatment-related ^b	30 (65.2%)	27 (61.4%)	39 (81.3%)
Serious	1 (2.2%)	2 (4.5%)	3 (6.3%)
TEAE leading to discontinuation	2 (4.3%)	1 (2.3%)	3 (6.3%)

Abbreviations: AE = adverse event; Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4) % of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event.

a. Subjects reporting more than 1 AE are counted only once within each treatment using the highest severity.

b. Subjects reporting more than 1 AE are counted only once within each treatment using the closest relationship to study drug. Related events include those reported as "Possible" or "Probable" relationship to study drug.

Source: Section 14.3.1.1.

Table 17: Summary of Treatment-Emergent Adverse Events by Preferred Term with Incidence in Either Treatment $\geq$ 5% (Study CL-P-19005, Safety Population)

MedDRA System Organ Class Preferred Term ^a	Treatment at Time of Onset		All Subjects (N = 48) n (%)
	Donepezil TDS Crystals (N = 46) n (%)	Donepezil TDS No Crystals (N = 44) n (%)	
Subjects with at least one TEAE	36 (78.3%)	31 (70.5%)	42 (87.5%)
Abnormal dreams	11 (23.9%)	12 (27.3%)	18 (37.5%)
Headache	12 (26.1%)	8 (18.2%)	15 (31.3%)
Application site pruritus	7 (15.2%)	5 (11.4%)	10 (20.8%)
Diarrhoea	4 (8.7%)	4 (9.1%)	8 (16.7%)
Nausea	5 (10.9%)	4 (9.1%)	7 (14.6%)
Back pain	1 (2.2%)	5 (11.4%)	6 (12.5%)
Dizziness	1 (2.2%)	3 (6.8%)	4 (8.3%)
Hypertension	3 (6.5%)	0	3 (6.3%)
Application site papules	3 (6.5%)	0	3 (6.3%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4) % of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; MedDRA = Medical Dictionary for Regulatory Activities; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event.

- a. Adverse events were classified into system organ class and preferred term using MedDRA Version 22.0. At each level of summarizations (any event, system organ class, and preferred term), subjects reporting more than one adverse event were counted only once within each treatment.

Source: Section 14.3.1.2.

Table 18: Summary of TEAEs by Maximum Reported Severity (Study CL-P-19005, Safety Population)

	Donepezil TDS Crystals (N = 46) n (%)	Donepezil TDS No Crystals (N = 44) n (%)	All Subjects (N = 48) n (%)
Subjects with at least one TEAE	36 (78.3%)	31 (70.5%)	42 (87.5%)
Mild	30 (65.2%)	28 (63.6%)	33 (68.8%)
Moderate	6 (13.0%)	2 (4.5%)	8 (16.7%)
Severe	0	1 (2.3%)	1 (2.1%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4) % of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; MedDRA = Medical Dictionary for Regulatory Activities; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event

Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event are counted only once within each treatment using the highest reported severity. Adverse events were coded to system organ class and preferred term using MedDRA version 22.0.

Source: Section 14.3.1.2, Section 14.3.1.5

Table 19: Summary of Drug-Related Treatment Emergent Adverse Events by Preferred Term with Incidence $\geq 5\%$ during Either Treatment (Study CL-P-19005, Safety Population)

Preferred Term ^a	Donepezil TDS Crystals (N = 46) n (%)	Donepezil TDS No Crystals (N = 44) n (%)	All Subjects (N = 48) n (%)
Subjects with at least one drug-related TEAE ^b	30 (65.2%)	27 (61.4%)	39 (81.3%)
Abnormal dreams	11 (23.9%)	12 (27.3%)	18 (37.5%)
Headache	7 (15.2%)	5 (11.4%)	11 (22.9%)
Application site pruritus	7 (15.2%)	5 (11.4%)	10 (20.8%)
Diarrhoea	3 (6.5%)	3 (6.8%)	6 (12.5%)
Nausea	4 (8.7%)	4 (9.1%)	6 (12.5%)
Application site papules	3 (6.5%)	0	3 (6.3%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; MedDRA = Medical Dictionary for Regulatory Activities; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event.

- a. Adverse events are classified into system organ class and preferred term using MedDRA Version 22.0. At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event are counted only once within each treatment using the closest relationship to study drug.
- b. Drug-related is defined as a possible or probable relationship to study drug.

Source: Section 14.3.1.2, Section 14.3.1.6.

Table 20: Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Study CL-P-19005, Safety Population)

MedDRA System Organ Class Preferred Term ^a	Donepezil TDS Crystals (N = 46) n (%)	Donepezil TDS No Crystals (N = 44) n (%)	All Subjects (N = 48) n (%)
Subjects with at least one serious TEAE	1 (2.2%)	2 (4.5%)	3 (6.3%)
Cardiac disorders	1 (2.2%)	1 (2.3%)	2 (4.2%)
Atrial fibrillation	1 (2.2%)	0	1 (2.1%)
Palpitations	0	1 (2.3%)	1 (2.1%)
Injury, poisoning and procedural complications	0	1 (2.3%)	1 (2.1%)
Foot fracture	0	1 (2.3%)	1 (2.1%)
Investigations	1 (2.2%)	1 (2.3%)	1 (2.1%)
Troponin I increased	1 (2.2%)	0	1 (2.1%)
Nervous system disorders	0	1 (2.3%)	1 (2.1%)
Dizziness	0	1 (2.3%)	1 (2.1%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; MedDRA = Medical Dictionary for Regulatory Activities; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event.

- a. Adverse events were classified into system organ class and preferred term using MedDRA Version 22.0. At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event were counted only once within each treatment using the closest relationship to study drug.

Source: Section 14.3.1.7.

Table 21: Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug and/or Study Discontinuation by System Organ Class and Preferred Term (Study CL-P-19005, Safety Population)

MedDRA System Organ Class Preferred Term ^a	Donepezil TDS Crystals (N = 46) n (%)	Donepezil TDS No Crystals (N = 44) n (%)	All Subjects (N = 48) n (%)
Subjects with at least one TEAE leading to study drug discontinuation and/or study discontinuation	2 (4.3%)	1 (2.3%)	3 (6.3%)
Cardiac disorders	1 (2.2%)	1 (2.3%)	2 (4.2%)
Atrial fibrillation	1 (2.2%)	0	1 (2.1%)
Palpitations	0	1 (2.3%)	1 (2.1%)
Investigations	1 (2.2%)	0	1 (2.1%)
Troponin I increased	1 (2.2%)	0	1 (2.1%)
Nervous system disorders	0	1 (2.3%)	1 (2.1%)
Dizziness	0	1 (2.3%)	1 (2.1%)
Skin and subcutaneous tissue disorders	1 (2.2%)	0	1 (2.1%)
Eczema	1 (2.2%)	0	1 (2.1%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; MedDRA = Medical Dictionary for Regulatory Activities; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event.

- a. Adverse events were classified into system organ class and preferred term using MedDRA Version 22.0. At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event were counted only once within each treatment using the closest relationship to study drug.

Source: Section 14.3.1.8.

Table 22: Summary of Treatment-Emergent Adverse Events Associated with the TDS Application Site in the System Organ Class of General Disorders and Administration Site Conditions by Preferred Term (Study CL-P-19005, Safety Population)

Preferred Term ^a	Donepezil TDS Crystals (N = 46) n (%)	Donepezil TDS No Crystals (N = 44) n (%)	All Subjects (N = 48) n (%)
Application site pruritus	7 (15.2%)	5 (11.4%)	10 (20.8%)
Application site papules	3 (6.5%)	0	3 (6.3%)
Application site irritation	0	2 (4.5%)	2 (4.2%)
Application site paraesthesia	0	2 (4.5%)	2 (4.2%)
Application site discolouration	1 (2.2%)	0	1 (2.1%)
Application site hypersensitivity	0	1 (2.3%)	1 (2.1%)
Application site pain	1 (2.2%)	0	1 (2.1%)
Application site urticaria	0	1 (2.3%)	1 (2.1%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; MedDRA = Medical Dictionary for Regulatory Activities; TDS = transdermal delivery system; TEAE = treatment-emergent adverse event

a. Adverse events are classified into system organ class and preferred term using MedDRA Version 22.0. At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event are counted only once within each treatment using the closest relationship to study drug.

Source: Section 14.3.1.9.

Table 23: Summary of Dermal Response Scores by Time Point (Study CL-P-19005, Skin Irritation Population)

Treatment	Time Point	Dermal Response Scores				
		0	1	2	3	≥4
Donepezil TDS Crystals (N=46)	Day 1, pre-application	46 (100%)	0	0	0	0
	0.5 hrs post removal	5 (10.9%)	28 (60.9%)	10 (21.7%)	3 (6.5%)	0
	24 hrs post removal	26 (56.5%)	11 (23.9%)	9 (19.6%)	0	0
	48 hrs post removal	32 (69.6%)	7 (15.2%)	7 (15.2%)	0	0
	72 hrs post removal	36 (78.3%)	5 (10.9%)	5 (10.9%)	0	0
Donepezil TDS No Crystals (N=44)	Day 1, pre-application	44 (100%)	0	0	0	0
	0.5 hrs post removal	4 (9.1%)	28 (63.6%)	9 (20.5%)	3 (6.8%)	0
	24 hrs post removal	24 (54.5%)	13 (29.5%)	6 (13.6%)	1 (2.3%)	0
	48 hrs post removal	25 (56.8%)	11 (25.0%)	4 (9.1%)	1 (2.3%)	0
	72 hrs post removal	35 (79.5%)	8 (18.2%)	1 (2.3%)	0	0

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; hrs = hours; TDS = transdermal delivery system.

Notes:

- Subjects whose patches were removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from visits following patch removal or detachment.
- Dermal response scores are defined as: 0 = no evidence of irritation; 1 = minimal erythema that is barely perceptible; 2 = definite erythema that is readily visible and minimal edema, or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema, and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond the application site.
- If a patch was removed due to excessive irritation, dermal response scores were imputed at scheduled assessments after patch removal using last available observation carried forward.

Source: Section 14.3.5.4.

Table 24: Summary of Other Effects Scores by Time Point (Study CL-P-19005, Skin Irritation Population)

Treatment	Time Point	Other Effects Scores				
		None (0)	A (0)	B (1)	C (2)	≥F (3)
Donepezil TDS Crystals (N=46)	Day 1, pre-application	22 (47.8%)	24 (52.2%)	0	0	0
	0.5 hrs post removal	22 (47.8%)	21 (45.7%)	0	3 (6.5%)	0
	24 hrs post removal	22 (47.8%)	24 (52.2%)	0	0	0
	48 hrs post removal	20 (43.5%)	26 (56.5%)	0	0	0
	72 hrs post removal	22 (47.8%)	24 (52.2%)	0	0	0
Donepezil TDS No Crystals (N=44)	Day 1, pre-application	20 (45.5%)	24 (54.5%)	0	0	0
	0.5 hrs post removal	20 (45.5%)	22 (50.0%)	0	2 (4.5%)	0
	24 hrs post removal	20 (45.5%)	24 (54.5%)	0	0	0
	48 hrs post removal	18 (40.9%)	23 (52.3%)	0	0	0
	72 hrs post removal	20 (45.5%)	24 (54.5%)	0	0	0

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; hrs = hours; TDS = transdermal delivery system.

Notes:

- Subjects whose patches were removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from visits following patch removal or detachment.
- Other effects scores are defined as: None (0) = no other effects observed; A (0) = slightly glazed appearance; B (1) = markedly glazed appearance; C (2) = glazing with peeling and cracking; F (3) = glazing with fissures; G (3) = film of dried serous exudate covering all or part of the TDS site; H (3) = small petechial erosions and/or scabs.
- If a patch was removed due to excessive irritation, dermal response scores were imputed at scheduled assessments after patch removal using last available observation carried forward.

Source: Section 14.3.5.5.

Table 25: Summary of Combined Skin Irritation Scores by Time Point (Study CL-P-19005, Skin Irritation Population)

Treatment	Time Point	Combined Skin Irritation Scores					
		0	1	2	3	4	≥5
Donepezil TDS Crystals (N=46)	Day 1, pre-application	46 (100%)	0	0	0	0	0
	0.5 hrs post removal	5 (10.9%)	28 (60.9%)	7 (15.2%)	3 (6.5%)	3 (6.5%)	0
	24 hrs post removal	26 (56.5%)	11 (23.9%)	9 (19.6%)	0	0	0
	48 hrs post removal	32 (69.6%)	7 (15.2%)	7 (15.2%)	0	0	0
	72 hrs post removal	36 (78.3%)	5 (10.9%)	5 (10.9%)	0	0	0
Number (%) of subjects with a score of ≥3 at 30 minutes post removal							6 (13.0%)
Number (%) of subjects with ≥1 score of ≥3 at any time point between 30 minutes and 72 hours post removal							6 (13.0%)
Donepezil TDS No Crystals (N=44)	Day 1, pre-application	44 (100%)	0	0	0	0	0
	0.5 hrs post removal	4 (9.1%)	28 (63.6%)	7 (15.9%)	3 (6.8%)	2 (4.5%)	0
	24 hrs post removal	24 (54.5%)	13 (29.5%)	6 (13.6%)	1 (2.3%)	0	0
	48 hrs post removal	25 (56.8%)	11 (25.0%)	4 (9.1%)	1 (2.3%)	0	0
	72 hrs post removal	35 (79.5%)	8 (18.2%)	1 (2.3%)	0	0	0
Number (%) of subjects with a score of ≥3 at 30 minutes post removal							5 (11.4%)
Number (%) of subjects with ≥1 score of ≥3 at any time point between 30 minutes and 72 hours post removal							5 (11.4%)

Abbreviations: Donepezil TDS Crystals = 10 mg per day Donepezil TDS with crystals covering (b) (4)% of the patch active delivery area; Donepezil TDS No Crystals = 10 mg per day Donepezil TDS with no crystals covering the patch active delivery area; hrs = hours; TDS = transdermal delivery system.

Notes:

- Subjects whose patches were removed early for reasons unrelated to skin tolerability or detached due to lack of adhesion are excluded from visits following patch removal or detachment.
- Combined skin irritation score is calculated as the sum of the dermal response and other effects scores.
- If a patch was removed due to excessive irritation, dermal response scores were imputed at scheduled assessments after patch removal using last available observation carried forward.

Source: Section 14.3.5.6, Section 14.3.5.7.

5. Conclusions of Chemistry Reviewer

I note that the Chemistry team consisting of Andrei Ponta in collaboration with Martha Heimann, in collaboration with additional Quality Team members consisting of Youmin Wang, Yubing Tang, Kaushalkumar Dave, Ta-Chen Wu, Erica Keafer, and Caroline Strasinger stated on March 3, 2022, in the overall Quality Team recommendations and conclusion on approvability that: "NDA 212304 for Adlarity (donepezil) transdermal system (TDS) is recommended for APPROVAL from a product quality perspective. In the NDA resubmission, the applicant adequately addressed the outstanding quality deficiencies communicated in the 7/23/2020 Complete Response Letter (CRL)."

6. Conclusions of Clinical Pharmacology Reviewer

I have reviewed the recommendations of the clinical pharmacology review team for this re-submission consisting of Min Li, Vishnu Sharma, Atul Bhattaram, and Bilal AbuAsal completed on March 7, 2022. In the recommendations section they state: "The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA (#212304) and recommended approval based on 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." I additionally note that OCP conducted pharmacokinetic simulations of switching from ARICEPT to ADLARITY and concluded that the first TDS patch should be applied when administering the last oral dose (b) (4)

7. Clinical Conclusions

After reviewing the clinical study reports submitted with this resubmission, I find that the sponsor has resolved deficiencies in the original submission, and I have no significant clinical safety arising after analysis of the newly completed studies.

In Study CL-P-20003, the sponsor evaluated the bioequivalence of steady-state pharmacokinetics of 5 mg/day and 10 mg/day Corplex Donepezil transdermal system manufactured with the commercial process (b) (4) compared to oral administration of 10 mg Aricept in healthy volunteers. I find that the study design was acceptable, using a Phase 1, open-label, randomized, 3-period, 3-treatment, crossover study. On reviewing the sponsor's table 19 from the report for study 20003, I note that in comparing the 10 mg/day transdermal delivery system applied weekly compared to 10 mg oral Aricept tablets, overall, the transdermal system had fewer TEAEs than oral Aricept. Of note, gastrointestinal side effects were significantly less in the 10 mg/day transdermal delivery system (14.5%) than 10 mg oral Aricept (53.6%). The 10 mg/day transdermal delivery system, however, did have increased treatment emergent adverse events relative to the 10 mg oral Aricept tablet with application site pruritis and dermatitis and a slight increase in musculoskeletal

and connective tissue disorders (12.7%) vs (10.7%), muscle spasms (9.1%) vs (8.9%), insomnia (7.3%) vs (0%), abnormal dreams (3.6%) vs (1.8%), and headache (14.5%) vs (12.5%). Overall, from a clinical safety perspective, I assess that when looking at the totality of the adverse events detected and frequency in the two arms, the 10 mg/day transdermal delivery system has no significant increased safety risk relative to 10 mg oral Aricept. While there are adverse events such as application site pruritis and dermatitis and that are uniquely elevated relative to an oral formulation, and the patch has some slight increases over Aricept in other adverse events, I note that reduction of gastrointestinal side effects is significant using the transdermal patch. Therefore, I would conclude that there is no increased overall safety risk using the transdermal patch formulation based on an overall assessment of adverse event profiles. The sponsor also provided an analysis of shifts in lab values from normal, and I agree with the sponsor that none of the shifts in lab values demonstrated a clinically meaningful pattern. Given the transdermal delivery system's increase in application site pruritis and dermatitis, I carefully reviewed the dermal response scores and other-effects scores following patch removal. For the dermal response scores for the 5 mg/day and 10 mg/day patches, I note that in most cases, they were rated at or below the level of 3 (erythema and papules) with a few cases being rated at 5 (erythema, edema, and papules). For the other-effects scores, I note that greater than 90% of patches had no other effects observed. Overall, I am reassured with the findings of the transdermal system as demonstrated through study CL-P-20003.

In Study CL-P-20004, the sponsor evaluated Corplex Donepezil TDS of different ages stored at 5°C and the relative bioavailability of Corplex Donepezil transdermal delivery system, which had been maintained at refrigerated storage conditions (2 to 8°C) for at least 18 months from its date of manufacture, to Corplex Donepezil transdermal delivery system manufactured with the commercial process, which had been maintained at refrigerated storage conditions (2 to 8°C) for approximately 6 months from its date of manufacture, in healthy volunteers after single-dose applications (1-week wear). The sponsor conducted a Phase 1, open-label, randomized, 2-period, 2-treatment, crossover pharmacokinetic study which is acceptable. I note that there were only 6 treatment emergent adverse events, all of which occurred in the treatment with the patches stored in refrigerated conditions for 18 months from date of manufacture, while none occurred in the patches stored for 6 months. Of these six, only two treatment emergent adverse events were deemed related to study treatment, which included chills and muscle spasms. The two treatment emergent adverse events that resulted in discontinuation of the subjects from the study product and early termination for the subjects from the study included muscle spasms and anxiety. I also note that four of the six treatment emergent adverse events were mild in severity with the two exceptions being nasopharyngitis and muscle spasms which were moderate. I note that no patches were removed due to an unacceptable degree of skin irritation. Overall I am reassured with the clinical safety findings of long-term refrigeration of the transdermal system as demonstrated through study CL-P-20004.

In Study CL-P-19005, the sponsor conducted a Phase 1, randomized, blinded, 2-way crossover study to assess the relative bioavailability of Corplex™ donepezil transdermal delivery systems with and without crystals. The primary objective of this study was to assess relative bioavailability of donepezil from single application of once-weekly Corplex™ Donepezil Transdermal Delivery Systems (TDS) with crystals (crystals covering (b) (4) % within the active delivery area) compared to Corplex Donepezil TDS without crystals, while the secondary objectives was to evaluate the safety and tolerability (including local skin irritation) of Corplex Donepezil TDS. I do note that, as the sponsor pointed out, headache, hypertension and application site papules had higher incidences (>5%) in the Donepezil TDS with crystals treatment while back pain had a higher incidence in the Donepezil TDS with no crystals treatment as noted in the sponsor's table 17; however, I do not find the difference between the two clinically compelling. Overall, on reviewing the results provided in the clinical study report for protocol CL-P-19005, I agree with the sponsor's conclusion that the presence (covering (b) (4) % of active delivery area of the patch) or absence of donepezil crystals does not affect drug delivery, pharmacokinetics, safety, or tolerability of the Corplex Donepezil TDS patch as demonstrated through the results of study CL-P-19005.

8. Recommendation

From a clinical safety perspective based on the data submitted in studies CL-P-20003, CL-P-20004, and CL-P-19005, I would recommend approval of Adlarity (donepezil transdermal system), also known as Corplex Donepezil Transdermal System, for the treatment of mild, moderate, and severe dementia of the Alzheimer's type.

The clinical pharmacology and chemistry reviews of this resubmission support that approval.

Brian Trummer, M.D., Ph.D.
Medical Reviewer

bt
cc:
HFD-120
IND

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/

BRIAN J TRUMMER
03/09/2022 01:50:50 PM
NDA

RANJIT B MANI
03/09/2022 01:52:41 PM

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	212,304 (includes information from IND 129,778)
Priority or Standard	Standard
Submit Date(s)	29 September 2019
Received Date(s)	30 September 2019
PDUFA Goal Date	30 July 2020
Division/Office	Division of Neurology Products / OND / CDER
Reviewer Name(s)	David A. Hosford, MD PhD
Review Completion Date	
Established/Proper Name	donepezil transdermal system
(Proposed) Trade Name	Adlarity
Applicant	Corium Inc.
Dosage Form(s)	transdermal patch
Applicant Proposed Dosing Regimen(s)	Two strengths: 1) a 52.5cm ² patch, worn for 7 days to deliver 5mg/day; 2) a 105cm ² patch, worn for 7 days to deliver 10mg/day
Applicant Proposed Indication(s)/Population(s)	symptomatic treatment of mild, moderate, and severe Alzheimer's dementia
Recommendation on Regulatory Action	I recommend that the product is not approved and that a CR letter be issued
Recommended Indication(s)/Population(s) (if applicable)	Treatment for dementia of the Alzheimer's type

Table of Contents

Glossary	7
1. Executive Summary	9
1.1. Product Introduction.....	9
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	9
1.3. Benefit-Risk Assessment	9
1.4. Patient Experience Data.....	13
2. Therapeutic Context.....	14
2.1. Analysis of Condition.....	15
2.2. Analysis of Current Treatment Options	16
3. Regulatory Background	16
3.1. U.S. Regulatory Actions and Marketing History	16
3.2. Summary of Pre-submission/Submission Regulatory Activity	17
3.3. Foreign Regulatory Actions and Marketing History	18
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	19
4.1. Office of Scientific Investigations (OSI)	19
4.2. Product Quality	19
4.3. Clinical Microbiology	19
4.4. Nonclinical Pharmacology/Toxicology	19
4.5. Clinical Pharmacology	20
4.6. Devices and Companion Diagnostic Issues	21
4.7. Consumer Study Reviews.....	21
5. Sources of Clinical Data and Review Strategy	22
5.1. Table of Clinical Studies	22
5.2. Review Strategy	27
6. Review of Relevant Individual Trials Used to Support Efficacy	27
7. Integrated Review of Effectiveness.....	27

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

7.1.	Assessment of Efficacy Across Trials	27
7.2.	Additional Efficacy Considerations.....	27
7.2.1.	Considerations on Benefit in the Post-market Setting	27
7.2.2.	Other Relevant Benefits.....	28
7.3.	Integrated Assessment of Effectiveness	28
8.	Review of Safety	28
8.1.	Safety Review Approach	28
8.2.	Review of the Safety Database	28
8.2.1.	Overall Exposure	29
8.2.2.	Relevant characteristics of the safety population:	29
8.2.3.	Adequacy of the safety database:	30
8.3.	Adequacy of Applicant's Clinical Safety Assessments.....	30
8.3.1.	Issues Regarding Data Integrity and Submission Quality.....	30
8.3.2.	Categorization of Adverse Events	30
8.3.3.	Routine Clinical Tests	31
8.4.	Safety Results	31
8.4.1.	Deaths	31
8.4.2.	Serious Adverse Events	31
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects.....	33
8.4.4.	Significant Adverse Events	34
8.4.5.	Treatment Emergent Adverse Events and Adverse Reactions	34
8.4.6.	Laboratory Findings	39
8.4.7.	Vital Signs.....	39
8.4.8.	Electrocardiograms (ECGs)	40
8.4.9.	QT	40
8.4.10.	Immunogenicity.....	40
8.5.	Analysis of Submission-Specific Safety Issues	41
8.5.1.	Patch Adhesion	41
8.5.2.	Skin Irritation and Sensitization	50
8.5.3.	Effect of Heat on PK Parameters, Combined Irritation Scores, and Adhesion.....	53

8.5.4. PK Parameters, Combined Irritation Scores, and Adhesion as a Function of Body Site Application	55
8.6. Safety Analyses by Demographic Subgroups	58
8.7. Specific Safety Studies/Clinical Trials	58
8.8. Additional Safety Explorations	59
8.8.1. Human Carcinogenicity or Tumor Development	59
8.8.2. Human Reproduction and Pregnancy	59
8.8.3. Pediatrics and Assessment of Effects on Growth	59
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound.....	59
8.9. Safety in the Post-market Setting	59
8.9.1. Safety Concerns Identified Through Post-market Experience	59
8.9.2. Expectations on Safety in the Post-market Setting	60
8.9.3. Additional Safety Issues From Other Disciplines	60
8.10. Integrated Assessment of Safety	61
9. Advisory Committee Meeting and Other External Consultations	61
10. Labeling Recommendations	61
10.1. Prescription Drug Labeling	61
10.2. Nonprescription Drug Labeling.....	62
11. Risk Evaluation and Mitigation Strategies (REMS)	62
12. Post-marketing Requirements and Commitments.....	63
13. Appendices	63
13.1. References.....	63
13.2. Financial Disclosure	64

Table of Tables

Table 1: PK parameters at steady state	19
Table 2. GMR ratios of PK parameters with and without heat	20
Table 3. Safety Database for All Trials	28
Table 4. Exposure to TDS	29
Table 5: IND Study Demographics	29
Table 6: SAEs in All Studies	31
Table 7: TEAE Profile of Studies 15086 and 16010	36
Table 8. TDS 5mg/day: Application Site Events	38
Table 9. TDS 10mg/day: Application Site Events	38
Table 10. Overall Patch Adhesion Scale for Study 15086	41
Table 11. Adhesion of Drug Delivery Area for Study 15086	42
Table 12. Overall Patch Adhesion Scores in Study 15086	42
Table 13. Proportion of Subjects with Overall Patch Adhesion Scores > 2 in Study 15086	43
Table 14. Mean Adhesion of Drug Delivery Area in Study 15086	44
Table 15. Proportion of Subjects with Drug Delivery Score > 5 in Study 15086	46
Table 16. Adhesion Assessment Scale for Study 16010	46
Table 17. Overall Patch Adhesion Scores and Proportion of Subjects > 5 in Study 16010	47
Table 18. Mean Adhesion of Drug Delivery Area and Proportion of Subjects > 5 in Study 16010	49
Table 19. Dermal Response Scale for Study 16011	50
Table 20. Other Effects Scale for Study 16011	50
Table 21. Combined Irritation Scores During Induction Phase in Study 16011	51
Table 22. Effects of Age, Gender, and Ethnicity on Combined Irritation Scores in Study 16011	52
Table 23. Plasma PK Parameters for Donepezil in the Presence or Absence of Heat in Study 16039	53
Table 24. Combined Irritation Scores in the Presence and Absence of Heat in Study 16039	54
Table 25. Adhesion as a Function of Heat in Study 16039	54
Table 26. Plasma PK Parameters for Donepezil as a Function of Application Site in Study 16012	55
Table 27. Mean Adhesion Scores for Drug Delivery Area as a Function of Application Site in Study 16012	56
Table 28. Combined Irritation Scores as a Function of Application Site in Study 16012	57
Table 29. Combined Irritation Scores as a Function of Age, Gender, and Ethnicity in Study 16011	58

Table of Figures

Figure 1. TEAEs by Treatment, Study 15086	34
Figure 2. TEAEs by Treatment, Study 16010	35

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TDS	transdermal delivery system (i.e., the Adlarity patch)
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Adlarity® (donepezil transdermal system [TDS]) is the proposed brand name for a donepezil patch formulation. Donepezil hydrochloride is an acetylcholinesterase inhibitor, and it is indicated for the treatment of Alzheimer's dementia. The sponsor proposes that Adlarity TDS will be indicated for the treatment of mild, moderate, and severe Alzheimer's dementia. The Adlarity TDS consists of topical skin patches of two strengths: 1) a 52.5 cm² patch that is applied to the back once per week and worn for 7 days to deliver 5mg donepezil per day; and 2) a 105 cm² patch that is applied to the back once per week and worn for 7 days to deliver 10mg donepezil per day.

Important Note:

Hereafter this review will typically refer to the Adlarity TDS as TDS.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This section does not apply for this 505(b)(2) application, which relies on a bioequivalence (BE) study for a bridge between the product and the reference listed drug. There are no efficacy data for this product.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Alzheimer's disease (AD) is a relentlessly progressive neurodegenerative disease that is ultimately fatal. The pathophysiological basis (bases) is (are) uncertain. Five orally administered symptomatic treatments have been approved by AD for the treatment of dementia of the Alzheimer's type. Four are acetylcholinesterase inhibitors (ACHEIs), and one is an inhibitor of ion flux through N-methyl-D-aspartate (NMDA) receptor-activated channels. One of these approved treatments is available for both oral and topical (patch) administration, and two of these approved agents may be co-administered as an approved combination treatment.

The approved treatments do not halt the progression of the condition. The four ACHEIs have a safety profile that includes a relatively high rate of gastrointestinal, musculoskeletal, and nervous system adverse events. An approved transdermal delivery system (i.e., a skin patch) for one of the ACHEIs (Exelon [rivastigmine]) appears to produce fewer adverse events in general. The approval of a skin patch for the most commonly prescribed ACHEI (i.e., Aricept [donepezil]) may offer three principal advantages: 1) weekly application of the patch compared to daily administration of oral Aricept, thereby representing a method of delivery that could lead to greater compliance for people with memory deficits; 2) less burdensome means of delivery as compared to oral delivery for people who have dysphagia as a symptom of the condition; and 3) the potential for a lower rate of gastrointestinal and nervous system events.

The Adlarity donepezil transdermal system (henceforth typically termed either "the product," or "TDS") appears to have bioequivalence to Aricept; the clinical pharmacology staff have written a more thorough review of this topic. Adhesion of the product during its weekly application period is acceptable, including following showering or application of heat. Skin irritation and sensitization due to patch application are generally tolerable. The product produced a lower rate of some but not all gastrointestinal and nervous system events than Aricept. From a clinical viewpoint, TDS offers a new treatment option with a number of advantages to oral Aricept.

However, the Product Quality review lists serious issues related to the relative ease with which the patch (b) (4) may be removed (b) (4). This increases the risk of accidental exposure of patients or caregivers to higher doses than intended if they touch the product (b) (4); and it also raises the risk of under-dosing a patient if the layers separate while the patch is being worn. Due to this significant and serious safety concern, I recommend that the product not be approved and that a CR be issued. There are no other issues with TDS from a purely clinical viewpoint as regards the studies that were submitted with this NDA.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Alzheimer's disease (AD) is a relentlessly progressive neurodegenerative disease that is ultimately fatal. - The pathophysiological basis (bases) of the disease is (are) uncertain. - Five orally administered symptomatic treatments have been approved by AD for the treatment of dementia of the Alzheimer's type. Four are acetylcholinesterase inhibitors (ACHEIs), and one is an inhibitor of ion flux through N-methyl-D-aspartate (NMDA) receptor-activated channels. - Because dysphagia is often present in people with AD, a method of drug administration that does not use the oral route could be helpful.	New treatments of AD are needed. One option could in principle be a transdermal delivery system (i.e., a patch) that bypasses the need for oral administration of approved treatments, thereby providing a potential benefit for people who have dysphagia as one manifestation of the condition.
Current Treatment Options	- Five orally administered symptomatic treatments have been approved by AD for the treatment of dementia of the Alzheimer's type. Four are acetylcholinesterase inhibitors (ACHEIs), and one is an inhibitor of ion flux through N-methyl-D-aspartate (NMDA) receptor-activated channels. - The approved treatments do not halt the progression of the condition.	The approval of a skin patch for the most commonly prescribed ACHEI (i.e., Aricept [donepezil]) may offer three principal advantages: 1) weekly application of the patch compared to daily oral Aricept, a situation that may lead to greater compliance for people

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The four ACHEIs have a safety profile that includes a high rate of gastrointestinal and nervous system adverse events. - An approved transdermal delivery system (i.e., a skin patch) for one of the ACHEIs (Exelon [rivastigmine]) appears to produce fewer adverse events in general than oral Exelon.	with memory deficits; 2) less burdensome means of delivery than oral delivery, thereby eliminating swallowing issues for people who have dysphagia as a symptom of the condition; and 3) the potential for a lower rate of gastrointestinal and nervous system events as compared to the oral formulation.
Benefit	- The product appears to have bioequivalence to Aricept [see Clinical Pharmacology review]. - Adhesion of the product during its weekly application period is acceptable, including following showering or application of heat. - Skin irritation and sensitization due to patch application are generally at low rates and therefore tolerable. - The product produced a lower rate of some but not all gastrointestinal and nervous system events as compared to oral Aricept.	The product appears to fulfill a number of needs for new treatments for this condition. It offers less burdensome application (i.e., weekly instead of daily); it avoids oral administration and hence issues in people with dysphagia; and it has lower rates of some gastrointestinal and nervous system events.
Risk and Risk Management	- The Product Quality staff and staff from other disciplines have raised a major product quality issue that is the basis for my recommendation that this product is not approved. The patch (b) (4) can separate (b) (4) at times, producing two potential risks: a) the intended daily dose is not delivered if this separation occurs while the patch is being worn by a patient; and b) accidental exposure of patients or caregivers to donepezil if they touch the product (b) (4). - There are no other issues from a purely clinical viewpoint as regards the results of the clinical studies that were submitted with the NDA.	The potential for the patch layers to separate is an unacceptable safety risk for patients and/or caregivers. I recommend that the product is not approved.

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

1.4. Patient Experience Data

APPEARS THIS WAY ON ORIGINAL

No patient experience data were submitted with this application.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerFO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
X	Patient experience data were not submitted as part of this application.	
☐		

2. Therapeutic Context

2.1. Analysis of Condition

Alzheimer's disease (AD) is a relentlessly progressive neurodegenerative disease that is ultimately fatal (Alzheimer's Association, 2020). The disease affects all demographic groups and both genders. Symptoms of the disease include a progressive memory loss, behavioral changes, a loss of executive function, a progressive deficit in language, and in later stages a loss of the ability to undertake normal activities of daily living. As the disease reaches its end-stage, a greater need for supportive care occurs, leading finally to a need for complete care. The disease is ultimately fatal.

Staging of AD in a particular patient is based upon the clinical severity of the disease and/or the results of neurological testing using a variety of rating scales. This categorization results in subdivision of AD into mild, moderate, or severe stages (Alzheimer's Association, 2020).

The social and financial burdens of AD are high. It has been estimated that approximately six million people in the US have AD, and this number is expected to grow to more than sixteen million by 2050. Caregivers of people with AD provide care that is valued at approximately \$200 billion, and by 2050 this cost may rise to more than \$1 trillion (Alzheimer's Association, 2020).

Although there are several rare familial forms that produce symptoms when people are in their fourth or fifth decade, the majority of people develop what is termed sporadic or late-onset AD, with a later onset than familial AD. As a whole, AD affects approximately 3% of people aged 65 – 74; approximately 17% of people aged 75-84; and approximately 32% of people who are 85 years of age or older (Hebert et al., 2013). AD or other types of dementia account for up to 1 in 3 deaths in elderly individuals (Alzheimer's Association, 2020). Due to its age-dependence, females account for a greater proportion of affected people due to the increased life expectancy of females compared to males in the general population.

As demonstrated by the increased prevalence of AD by age, age is an important risk factor for the development of AD. Other risk factors include carriage of the E4 subtype of the apolipoprotein E (APOE) gene (Saunders et al., 1993), and a family history of AD (Mayeux et al., 1991).

Approved orally available treatments of AD include four acetylcholinesterase inhibitors (ACHEIs): Cognex (tacrine); Aricept (donepezil); Exelon (rivastigmine); and Razadyne (galantamine). There is also an approved inhibitor of ion flux through N-methyl-D-aspartate (NMDA) receptor-activated cation channels: Namenda (memantine). Cognex has been discontinued in the US due to its safety risks. One of these treatments (Exelon) is also available as a transdermal delivery system (i.e., a skin patch), and two of these treatments have been combined into a combination product (Namenda and Aricept). Each of these treatments or

combination treatments is purely symptomatic and therefore none of the approved treatments halt progression of the disease (Alzheimer's Association, 2020).

The most common adverse events that are associated with ACHEI treatments include events that affect the gastrointestinal system (e.g., nausea, vomiting, abdominal pain, diarrhea, or constipation), the central nervous system (e.g., somnolence or insomnia, abnormal dreams, nightmares), and the musculoskeletal system (e.g., muscle cramps or muscle spasms). These and other less common adverse events were reported during the pivotal approval studies and have been reported in the post-marketing environment, as listed in the Aricept, Exelon, and Razadyne Prescribing Information.

The unmet medical need is for new treatments that reduce or halt the development of the disease in pre-symptomatic people, and that halt disease progression in those affected by the disease. There is also a need for new symptomatic treatments that have better efficacy or safety profiles than currently approved products. As an example of the medical need for new symptomatic treatments, patch formulations may increase patient compliance, and they may decrease the difficulty that some patients have swallowing an oral product due to dysphagia, a common sign in people with AD. In principle, patch formulations of ACHEIs may also produce greater tolerability, as exemplified by a reduced rate of some but not gastrointestinal and central nervous system events in people who use the Exelon patch as compared to those who use oral Exelon.

2.2. Analysis of Current Treatment Options

See the list of approved treatments for AD in the section above. Aricept was approved in 1996; Exelon capsules were approved in 2000; Razadyne was approved in 2001; and Namenda was approved in 2003. The Exelon patch was approved in 2007.

There are no clinical data from adequate and well-controlled trials that support the use of unapproved treatments that are sometimes used by patients. These unapproved agents include ginkgo biloba, alpha tocopherol (i.e., Vitamin E), and a number of commercially available and/or over-the-counter agents.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

See the approval dates for the ACHEIs and for Namenda in section 2.2. TDS is not approved in any region.

3.2. Summary of Pre-submission/Submission Regulatory Activity

Pre-submission activity was conducted for IND 129,778, which is for Corplex in the treatment of mild, moderate, and severe AD. Corplex was the sponsor's original name for TDS before the sponsor-requested name of Adlarity was granted.

There were four pre-submission meetings, with key clinical issues discussed as summarized below. Other Nonclinical and Product Quality issues are discussed by the reviews of those disciplines.

- PIND meeting minutes were issued on 4/28/16. The primary topic of clinical discussion was that a clinical efficacy and safety study would likely not be required if TDS showed bioequivalence to oral donepezil; but also that the sponsor was strongly recommended to conduct such a clinical study anyway, should BE not be demonstrated.
- The Study May Proceed letter was issued on 10/18/16. The proposed study was a BE study that compared oral donepezil to TDS (study 15086). There was relatively little clinical material in this letter.
- The EOP2 meeting minutes were issued on 9/22/17. Principal areas of clinical discussion included those listed below. Note that some topics covered under "Clinical Questions" are actually more relevant to Clinical Pharmacology.
 - o Study 15086 may in principle be the sole study used to demonstrate BE of TDS to oral donepezil.
 - o [REDACTED] (b) (4)
 - o Details of the sponsor's dose-proportionality calculations are needed to support the sponsor's position that a separate dose-proportionality study is not required.
 - o The design of the TDS BE study (15086) appears adequate to support the assessment of TDS adhesion, but this is a matter of review once all adhesion results are evaluated.
 - o In response to the sponsor's stance that a donepezil-to-TDS switching study is not required, FDA asked the sponsor to perform a PK simulation study of oral donepezil to TDA to show that exposure differences will have no impact on clinical effectiveness.
 - o The designs of the skin irritation and skin sensitization studies appear sufficient, but this will be a matter of review once all results are

- evaluated.
- o The design of a donepezil bioavailability study to assess any difference based upon TDA application to different body regions (e.g., back, buttocks, and abdomen) appears sufficient, but this will be a review matter upon receipt of results.
 - o FDA stated that the effect of heat on TDS should be assessed (e.g., after a heating pad is applied).
 - o (b) (4).
 - o A 505(b)(2) application may rely upon efficacy/safety data contained in FDA-approved labelling for the listed drug.
- The pre-NDA meeting minutes were issued on 10/14/18. Principal areas of clinical/submission agreement are summarized below.
 - o Key clinical studies will be the BE study 15086, the skin irritation and skin sensitization study 16011, the study of bioavailability when the product is applied to different body regions (study 16012), and the study that evaluates the effect of heat (study 16039).
 - o The Summary of Clinical Safety and the Integrated Summary of Safety will consist of the study reports for individual studies and no integrated dataset.
 - o Integrated skin tolerability data will be derived from five studies (16010, 16011, 16012, 16039, and 15086).
 - o A comparison of TEAEs from healthy volunteers who applied TDS to those of ARICEPT in the pivotal approval studies will be made using a table.

As regards regulatory activity for the active moiety of TDS, donepezil hydrochloride, this product is marketed in many regions including the US under the brand name of Aricept. In 1996, Aricept (tablets of 5mg and 10mg strengths) was approved in the US for the treatment of mild to moderate Alzheimer's disease. An orally disintegrating formulation of Aricept was approved in the US in 2004. In 2006 the indication for Aricept was extended to severe Alzheimer's disease (using the 10mg tablet) in the US. An Aricept strength of 23mg in an extended release form was approved in 2010 in the US for the treatment of Alzheimer's disease ((b) (4) moderate, and severe). Aricept was approved in many other regulatory regions after its US approval. It is now available in orally administered generic forms in both tablet and extended release formulations, but not in a transdermal formulation. It is also available as an approved combination product, in which both donepezil and memantine are co-administered.

3.3. Foreign Regulatory Actions and Marketing History

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

See section 3.2 above for the important regulatory milestones of Aricept and its generic versions. Aricept is now approved in more than 90 countries, and it has not been withdrawn from any region.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

This section is not applicable to TDS because no OSI investigation or audits have been made.

4.2. Product Quality

Formal product quality information and assessments are provided in reviews by this discipline by other staff. A major product quality issue is the relative ease of separation of the patch [REDACTED] (b) (4). This issue has been observed with every batch received from the sponsor. Because of this issue, I recommend that the product is not approved and that a CR is issued. There is an unacceptable potential risk for over-exposure to donepezil if patients or caregivers touch the exposed product [REDACTED] (b) (4), and a risk of altered dosing of donepezil if the patch layers separates when the product is being worn.

The pivotal bioequivalence (BE) study used the to-be-marketed TDS sizes (i.e., 52.5cm² to deliver 5mg/day and 105cm² to deliver 10mg/day). Some of the earlier studies in which safety information was collected used TDS sizes that did not differ significantly in size from those cited above, and all of these different sizes delivered either 5mg/day or 10mg/day.

4.3. Clinical Microbiology

The TDS has not been tested in microbiology studies. In agreement with communications between the Division of Neurology Products and the sponsor, all nonclinical data relevant to TDS stem from public literature regarding Aricept or generic donepezil formulations.

4.4. Nonclinical Pharmacology/Toxicology

The TDS has not been tested in pharmacology or toxicology studies. All relevant nonclinical data stem from public literature regarding Aricept or generic donepezil formulations.

4.5. Clinical Pharmacology

In BE study 15086, PK parameters of TDS patch A (to-be-marketed patch with an area of 105cm², to deliver 10mg/day) and TDS patch B (area of 130cm², to deliver 10mg/day) were compared to those of oral donepezil (10mg daily) at steady-state, five weeks after the onset of dosing. The following sponsor-derived table shows the geometric mean ratios (GMRs) between the two patches (A and B) vs. oral donepezil (C). Note that the 90% confidence intervals (CIs) for the ratios of GMRs for C_{max} and for AUC_{0-168hrs} appear to reside within the 0.80 to 1.25 window that constitutes evidence for BE. See the Clinical Pharmacology review for an in-depth discussion of this study and of these results.

Table 1: PK parameters at steady state

Treatment	n	Adjusted Geometric Mean ^a	Comparison	Adjusted GMR	90% CI ^{b,c}
<u>AUC_{0-168,ss} (h*ng/mL)</u>					
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			
<u>C_{max,ss} (ng/mL)</u>					
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_{0-168,ss} = area under the plasma concentration-time curve during a 1-week period, at steady-state. For oral administration (Aricept 10 mg), AUC_{0-168,ss} equals area under the plasma concentration-time curve from zero to 24 hours for Day 7 during steady-state Week 5 (AUC₀₋₂₄) 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 cm² (10 mg/day donepezil); TDS B = Corplex Donepezil TDS 130 cm² (10 mg/day donepezil).

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 0.80 to 1.25.

- Adjusted geometric mean is the exponentiated LSM of the natural log-transformed values.
- Estimates of the adjusted GMR confidence limits were exponentiated.
- 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: Study 15086 CSR, Table 27]

In a separate study (16039), application of heat to TDS by a heating pad was shown to have no significant effect on C_{max} and AUC₀₋₁₆₈ of the to-be-marketed TDS patch of 52.5cm² (to deliver 5mg/day). The results are shown in the following sponsor-derived table. Note that the GMR ratios for these parameters following heat vs. no heat appear to be within or equal to the 0.80

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

to 1.25 ratios that establish BE.

Table 2. GMR ratios of PK parameters with and without heat

Treatment	n	Adjusted Geometric Mean ^a	Comparison	Adjusted GMR	P-value	90% Confidence Interval
AUC₀₋₁₆₈ (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				

[Source: Study 16039 CSR, Table 24]

4.6. Devices and Companion Diagnostic Issues

There is no companion device or diagnostic.

4.7. Consumer Study Reviews

No label comprehension, patient self-selection, or other human factors studies were evaluated by a social science reviewer or by the Division of Medication Error Prevention and Analysis.

There are no issues relevant to this topic in this medical reviewer's opinion.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Nine studies of TDS were conducted; three were conducted in Australia and hence not under the IND, and six were conducted in the US under the IND (IND 129,778). One of the IND studies (15086) also had a sub-study that is considered by the sponsor to represent a separate study, and therefore it is handled below as a separate study.

A table is inadequate to convey the detailed information required for each study. For that reason, descriptions are in text format (below) for each study that was submitted in the application.

Study 15007

- Study location
 - o Australia (non-IND)
- Study start and completion dates
 - o Aug 2015 – Mar 2016
- Study design
 - o Open-label, cross-over and sequential
- Treatment population
 - o Healthy adults, 50 – 79 years of age
- Treatment dosage regimen and route of administration
 - o 50cm² patches with different release characteristics, and oral Aricept (5mg or 10mg)
- Treatment duration
 - o Single patch worn for one week vs. daily oral Aricept for 7 days
- Number of subjects dosed
 - o 19 subjects, 8 males and 11 females
- Key objectives
 - o Formulation selection

Study 15081

- Study location
 - o Australia (non-IND)
- Study start and completion dates
 - o Feb 2016 – Jun 2016

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

- Study design
 - Open-label, parallel and cross-over
- Treatment population
 - Healthy females, 51-78 years of age
- Treatment dosage regimen and route of administration
 - 60cm² patches with three formulations, and oral Aricept (5mg or 10mg)
- Treatment duration
 - Single patch worn for one week vs. daily Aricept for 7 days
- Number of subjects dosed
 - 26 females
- Key objectives
 - Finalize formulation decision

Study 16007

- Study location
 - Australia (non-IND)
- Study start and completion dates
 - Jun 2016 – Nov 2016
- Study design
 - Open-label sequential
- Treatment population
 - Healthy adults (50 – 75 years of age)
- Treatment dosage regimen and route of administration
 - Two patch sizes (105cm² and 130 cm²) with different overlay types, using oral Aricept (5mg) for titration prior to patch application
- Treatment duration
 - One patch applied weekly
- Number of subjects dosed
 - 14 males and 16 females
- Key objectives
 - Patch adhesion optimization and final patch decision

Study 15086

- Study location
 - US (IND 129,778)
- Study start and completion dates
 - Nov 2016 – May 2017
- Study design
 - Open-label, three-way crossover

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

- Treatment population
 - o Healthy adults (24 – 78 years of age)
- Treatment dosage regimen and route of administration
 - o Treatment A: 50cm² patch (lead-in) followed by 105cm²
 - o Treatment B: 50cm² patch (lead-in) followed by 130cm²
 - o Treatment C: oral Aricept, 5mg (lead-in) followed by 10mg
- Treatment duration
 - o 28 days of patches, applied once-weekly, or 28 days of daily oral Aricept
- Number of subjects dosed
 - o 34 males and 26 females
- Key objectives
 - o BE at steady state
 - o Safety and tolerability
 - o Patch adhesion

Study 15086 sub-study

- Study location
 - o US (IND 129,778)
- Study start and completion dates
 - o Apr 2017 – Aug 2017
- Study design
 - o Open-label, crossover
- Treatment population
 - o Healthy adults
- Treatment dosage regimen and route of administration
 - o Two different patches of 50cm², containing donepezil from two different API suppliers
- Treatment duration
 - o Single application of patch, worn for 7 days
- Number of subjects dosed
 - o 34 males and 13 females
- Key objectives
 - o Relative bioavailability of donepezil as a function of the API supplier

Study 16010

- Study location
 - o US (IND 129,778)
- Study start and completion dates

- o Oct 2017 – Mar 2018
- Study design
 - o Open-label, cross-over
- Treatment population
 - o Healthy adults (33 – 72 years of age)
- Treatment dosage regimen and route of administration
 - o TDS 53cm² (lead-in) followed by TDS 107cm², or oral Aricept 5mg (lead-in) followed by Aricept 10mg
- Treatment duration
 - o Following the 1-week lead-in, treatment durations for TDS is 28 days with once-weekly application; and 28 days of Aricept dosed orally once daily
- Number of subjects dosed
 - o 39 males and 47 females
- Key objectives
 - o Safety and tolerability
 - o Patch adhesion
 - o Originally this study was to be a second BE study to evaluate as a replication of BE study 15086. In the EOP2 minutes (9/22/17), the results of BE from study 15086 are in principle sufficient to show BE as the sole study for approval purposes. Hence, although PK sampling was performed in study 16010, no PK analyses are provided in the study 16010 study report.

Study 16011

- Study location
 - o US (IND 129,778)
- Study start and completion dates
 - o Nov 2017 – Apr 2018
- Study design
 - o Double-blind
- Treatment population
 - o Healthy adults (40 – 81 years of age)
- Treatment dosage regimen and route of administration
 - o TDS 53cm² (to deliver 5mg donepezil daily) or a patch of the same area but containing vehicle rather than donepezil
- Treatment duration
 - o Once-weekly patch applications
- Number of subjects dosed
 - o 104 male and 152 females
- Key objectives

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

- o Skin irritation and sensitization

Study 16012

- Study location
 - o US (IND 129,778)
- Study start and completion dates
 - o Jan 2018 – Jun 2018
- Study design
 - o Open-label, cross-over
- Treatment population
 - o Healthy adults
- Treatment dosage regimen and route of administration
 - o TDS 107 cm² applied to back
 - o TDS 107cm² applied to thigh
 - o TDS 107cm² applied to buttock
- Treatment duration
 - o Single application of patch, worn for 7 days
- Number of subjects dosed
 - o 35 males and 31 females
- Key objectives
 - o Relative bioavailability of donepezil as a function of anatomic site of patch application

Study 16039

- Study location
 - o US (IND 129,778)
- Study start and completion dates
 - o Feb 2018 – Jun 2018
- Study design
 - o Open-label, crossover
- Treatment population
 - o Healthy adults
- Treatment dosage regimen and route of administration
 - o TDS 53.5cm² with applied heat
 - o TDS 53.5cm² without applied heat
- Treatment duration
 - o Single patch application, worn for 7 days
- Number of subjects dosed

- o 12 males and 12 females
- Key objectives
 - o Relative bioavailability as a function of presence or absence of heat at the patch application site

5.2. Review Strategy

There are no efficacy studies in this 505(b)(2) application, and hence there are no statistical comparisons of data. The safety and tolerability data from each study will be considered separately in section 8. No pooled analyses of safety data will be reviewed because each study used a different design and had different objectives; pooling would cloud interpretation of the data. This safety presentation strategy (i.e., a lack of submission of pooled safety data) was proposed by the sponsor and in principle agreed with FDA in the pre-NDA meeting (minutes issued 10/4/18).

6. Review of Relevant Individual Trials Used to Support Efficacy

There are no efficacy studies in this 505(b)(2) application, and hence sections 6 and 7 are not relevant to this application.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There are no efficacy trials in this 505(b)(2) application and hence section 7 is irrelevant.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-market Setting

There are no efficacy trials in this 505(b)(2) application and hence section 7 is irrelevant.

7.2.2. Other Relevant Benefits

There are no efficacy trials in this 505(b)(2) application and hence section 7 is irrelevant.

7.3. Integrated Assessment of Effectiveness

There are no efficacy trials in this 505(b)(2) application and hence section 7 is irrelevant.

8. Review of Safety

8.1. Safety Review Approach

The overall approach to this safety review is to evaluate safety and tolerability issues separately for each of the nine studies that are listed in section 5.1. Each study had a distinctly different design and purpose and therefore no pooled analyses are helpful. In the pre-NDA meeting, the sponsor agreed with FDA, in principle, that provision of individual study safety results rather than pooled analyses would be acceptable for this NDA submission (Pre-NDA meeting minutes issued 10/4/18).

Because TDS contains donepezil hydrochloride as the active agent, the class pharmacology for acetylcholinesterase inhibitors (AChEIs) is relevant. The most common treatment-emergent adverse events (TEAEs) in the approval studies of Aricept and in its use in the clinic affect the gastrointestinal system (e.g., nausea, vomiting, diarrhea, constipation), the central nervous system (e.g., insomnia, abnormal dreams, nightmares, dizziness, and somnolence), or the musculoskeletal system (i.e., muscle cramps or spasms). All TEAEs reported in the submitted studies of TDS were evaluated, with an additional focus on those cited above.

TDS was designed applied to the back and left in place for a full week before a new patch is applied. Patch adhesion, skin irritation, and skin sensitization are potential issues, and therefore these types of events are evaluated with additional focus in section 8.5.

Finally, the effects of heat on TDS, or on the body site of TDS application, are also relevant for use in an outpatient setting. These issues will also be covered in Section 8.5.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In the nine trials conducted, 609 healthy adults were enrolled and received at least one treatment (either TDS at one of two daily delivery doses, oral Aricept at one of two doses, or a vehicle patch).

Table 3. Safety Database for All Trials

Safety Database for Trials of ATDS Individuals exposed to any treatment in this development program: N= 609 (N is the sum of unique subjects and hence differs from n in the columns below)			
Clinical Trial Groups	ATDS, any dose (n= 609)	Aricept tablets, any dose (active control) (n= 216)	Vehicle patch (placebo) (n= 256)
Healthy volunteers	609 ¹	216	256
Controlled trials conducted for this indication ²	472	216	256
All other trials conducted for this indication	137	0	0

¹ Some unique subjects were in more than one treatment arm, and therefore the sum of n in each cell is greater than 609 unique subjects.

² includes active controls using Aricept tablets (5 or 10 mg) and a placebo control consisting of a vehicle-containing patch

[Source: CSRs for each study. Note that the sponsor has referred to TDS as ATDS in this table.]

Table 4. Exposure to TDS

Dose of donepezil delivered daily ^{1,2}	7 days	14 days	21 days	35 days
5mg daily	N = 19	N = 90	N = 256	N = 9
10mg daily	N = 37	N = 0	N = 66	N = 196

¹ TDS patches of several different areas were used in the studies, but all patch sizes delivered either 5gm donepezil or 10mg donepezil daily.

² Some subjects were exposed to more than one TDS strength, hence the total n from every cell is greater than 609 unique subjects.

[Source: CSRs for each study]

8.2.2. Relevant characteristics of the safety population:

As per tables above, the safety population in the TDS development program consisted of 609 unique subjects. The race was predominantly white and the ethnicity was predominantly non-Hispanic/non-Latino. There were more females (54%) than males. The age range across the

nine studies was 20 – 82 years, but the majority of subjects were more than 50 years of age. The table below displays subject demographics for the six IND studies.

Table 5: IND Study Demographics

	15007 N=19 n (%)	15081 N=26 n (%)	16007 N=30 n (%)	15086 N=60 n (%)	15086 Sub-Study N=47 n (%)	16010 N=86 n (%)	16011 N=256 n (%)	16012 N=66 n (%)	16039 N=24 n (%)
Sex									
M	8 (42.1%)	0 (0.0%)	14 (46.7%)	34 (56.7%)	34 (72.3%)	39 (45.3%)	104 (40.6%)	35 (53.0%)	12 (50.0%)
F	11 (57.9%)	26 (100%)	16 (53.3%)	26 (43.3%)	13 (27.7%)	47 (54.7%)	152 (59.4%)	31 (47.0%)	12 (50.0%)
Age*									
≥ 65	14 (73.7%)	12 (46.2%)	9 (30.0%)	10 (16.7%)	0 (0.0%)	12 (14.0%)	41 (16.0%)	11 (16.7%)	6 (25.0%)
< 65	5 (26.3%)	14 (53.8%)	21 (70.0%)	50 (83.3%)	47 (100%)	74 (86.0%)	215 (84.0%)	55 (83.3%)	18 (75.0%)
Race									
White	18 (94.7%)	26 (100%)	30 (100%)	59 (98.3%)	47 (100%)	86 (100%)	254 (99.2%)	66 (100%)	24 (100%)
Other	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity									
Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)	15 (25.0%)	13 (27.7%)	18 (20.9%)	72 (28.1%)	16 (24.2%)	0 (0.0%)
Non-Latino	19 (100%)	26 (100%)	30 (100%)	45 (75.0%)	34 (72.3%)	68 (79.1%)	184 (71.9%)	50 (75.8%)	24 (100%)

Abbreviation: N=number of subjects included in the Safety Population, defined as all enrolled subjects who received at least one dose of study drug;
n=number of subjects in a subgroup of each study

[Source: Summary of Clinical Safety]

8.2.3. Adequacy of the safety database:

Although race and ethnicity were not as diversified as gender, there was sufficient representation of a non-white population to permit observations about an association of intrinsic factors with PK parameters or with safety findings. It is acceptable that there was a slight majority of females in these studies in healthy adults, because the intended population for the use of the product (i.e., people with AD) has a higher female predominance.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The studies were conducted in either Australia or the US, each of which has similar medical standards and adverse event reporting rates. The rates of TEAEs are consistent with anticipated rates based on the duration of the trials (i.e., at most 35 days of treatment). There are no apparent issues regarding data integrity.

8.3.2. Categorization of Adverse Events

TEAEs were reported from the time of study entry until the final visit, or up to 28 days following the last visit for any subjects who withdrew from the study early. All events were coded by a recent version of MedDRA.

The manner by which adverse events were elicited is not provided by the sponsor. In addition, there is no definition of adverse event categorization (e.g., the basis for assessments of severity or causality, and whether the event is serious or non-serious) in the protocols. However, mitigating this lack of information, all studies were conducted at a single site in Australia (studies 15007, 15081, and 16007) or by a single study center in the US (six IND studies, at Celerion, Inc.). It is therefore likely that the three non-IND studies conducted in Australia handled adverse event collection in a similar way, and also that the six IND studies handled them in a similar manner. Because safety evaluations of the studies for the purpose of this review were conducted on a study-by-study basis rather in a pooled fashion, there is no possibility that any differences in adverse event collection or categorization between the Australian and US sites could cloud their interpretation.

8.3.3. Routine Clinical Tests

The studies in the TDS development program had treatment periods that were at most 35 days. Laboratory assessments were typically made after 7 days (i.e., at the end of the 7-day treatment periods of the shorter studies) and again at the end of the study (i.e., at 14, 21, or 35 days depending on the length of the longer studies). This frequency of lab assessments during the TDS program is adequate because the safety profile of donepezil is well-known, and because there are no laboratory-related Warnings or Precautions for Aricept.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in the nine clinical trials conducted as a part of the TDS development program.

8.4.2. Serious Adverse Events

There were five SAEs across all of the studies. Below is the listing of these SAEs per MedDRA hierarchy, followed by a list of the SAEs along with brief points about each event.

Table 6: SAEs in All Studies

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Treat-ment at Time	System Organ Class/Preferred Term/Adverse Event	Onset Date/Time (Study Day)	Resolution Date/Time (Study Day)	Relation-ship to Study Drug	Action Taken with Study Drug	Medication or Treatment	Outcome	TEAE [1]
(b) (6)	C Hepatobiliary Disorders/Cholecystitis	Yes/3 (15)	(b) (6) (18)	SevereNotRelated	Drug Withdrawn	Concomitant Medication, Other: cholecystectomy	Recovered/Resolved	Yes
	B General Disorders and Administration Site Conditions/Chest Pain/Atypical Chest Pain	Yes/3 (19)	(b) (6) (19)	SeverePossibly Related	Drug Withdrawn	Concomitant Medication	Recovered/Resolved	Yes
Donepezil TDS	Injury, poisoning and procedural complications/Contusion/CONTUSION DUE TO ASSAULT, RIGHT KNEE	Yes /3 (2) (b) (6) (71)	(b) (6) (78)	ModerateNot Related	Dose Not Changed	None	Recovered/Resolved	Yes
	Injury, poisoning and procedural complications/Nail avulsion/AVULSION DUE TO TRAUMA, LEFT GREAT TOENAIL	Yes /3 (2) (b) (6) (71)	(b) (6) (92)	ModerateNot Related	Dose Not Changed	Concomitant Medication	Recovered/Resolved	Yes
B	Cardiac disorders/Atrial fibrillation/PAROXYSMAL ATRIAL FIBRILLATION	Yes /3 (b) (6) (46)	(b) (6) (47)	Moderate Not Related	Drug Withdrawn	Concomitant Medication	Recovered/Resolved	Yes

[Source: Listings for each study]

- Study 15086
 - Subject P-15086- (b) (6)
 - Serious event term (SOC): cholecystitis (Hepatobiliary Disorders)
 - Treatment at time of event: oral donepezil
 - Subject P-15086- (b) (6)
 - Serious event term (SOC): atypical chest pain (General Disorders and Administration Site Conditions)
 - Simultaneous non-serious adverse event (SOC): aching bilateral shoulders (Musculoskeletal and Connective Tissue Disorders)
 - History of mitral valve prolapse
 - Multiple other somatic complaints during treatment, including bilateral shoulder pain, aching in right arm, paresthesias in right arm, twitching in both legs
 - Treated with nitroglycerin and aspirin; no evidence of ischemia
 - Treatment at time of event: TDS, 130cm², to deliver 10mg/day
- Study 16010
 - Subject P-16010- (b) (6)
 - Two SAEs – event term (SOC):
 - Contusion due to assault, right knee (Injury, Poisoning, and Procedural Complications)

- Avulsion due to trauma, left great toenail (Injury, Poisoning, and Procedural Complications)
 - Treatment at time of events: TDS, 53.5 cm², to deliver 5mg/day
- Study 16012
 - o Subject (b) (6)
 - Event term (SOC):
 - Atrial fibrillation (Cardiac Disorders)
 - Relevant cardiac risk factors include older age (53 years) and gender (male)
 - Findings of left ventricular hypertrophy and dilated left atrium
 - Treatment at time of event: TDS, 107 cm², to deliver 10mg/day

The overall rate of the five SAEs across all study populations is low (0.8% [5/609]). The rate in subjects receiving oral Aricept in the approval studies (0.5% [1/216], per Aricept label) is similar to that in subjects receiving TDS (0.7% [4/609]; note that one subject had two SAEs). In this reviewer's opinion, none of the events that occurred in subjects receiving TDS are drug-related. Two of the four events stemmed from trauma afflicted upon the subject; a third event (musculoskeletal [atypical] chest pain) is both common in the general population and occurred in a subject with multiple somatic complaints; a fourth event (cholecystitis) is also common in the general population; and the fifth event (paroxysmal atrial fibrillation) occurred in a subject with both cardiac risk factors and with anatomic abnormalities in two chambers of the heart.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Across the six IND studies, there were 17 subjects who withdrew due to adverse events. These events included:

- Study 15086
 - o Subject P-15086 (b) (6) atrial fibrillation (treatment with oral donepezil)
 - o Subject P-15086 (b) (6) cholecystitis (treatment with oral donepezil)
 - o Subject P-15086 (b) (6) atypical chest pain (treatment with TDS, 130cm²)
- Study 16011
 - o Ten subjects with elevated blood pressure (all treated with TDS, 53.5cm², to deliver 5mg/day):
 - P-16011- (b) (6)
 - o P-16011- (b) (6): application site discharge (treated with TDS, 53.5cm², to deliver 5mg/day).
- Study 16012

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

- o (b) (6): atrial fibrillation (on TDS, 107cm² to deliver 10mg/day)
- o (b) (6): delusion (on TDS, 107cm²)
- Study 16039
 - o (b) (6): contact dermatitis (on TDS, 53.5cm² to deliver 5mg/day)

Of these 17 adverse events leading to withdrawal, the two events of delusions and contact dermatitis may have been related to TDS in this reviewer's opinion. The other 15 events were likely not related to TDS (13 events in 15 subjects) or to oral donepezil (2 events in 2 subjects).

As regards the 10 subjects with events of elevated blood pressure leading to withdrawal in study 16011, this event occurred at a rate of 3.9% (10/256). The Aricept Prescribing Information shows a rate of reported hypertension in 3% of subjects in the product's approval studies, and the Exelon patch prescribing information also shows a rate of reported hypertension in 3% of subjects in its approval studies. Thus, the rate of reported elevated blood pressure in subjects treated with TDS in study 16011 is similar to the rates that could be anticipated based upon the labeled rates for oral Aricept and for the Exelon patch.

There were no protocol-specified withdrawal criteria for any type of event in any study.

8.4.4. Significant Adverse Events

Across all IND studies, one subject (P-15086-(b) (6)) reported an adverse event of decreased neutrophil count while on treatment with TDS (105cm² to deliver 10mg/day). The subject had a history of immune system disorders. At Screening the neutrophil count was $2.3 \times 10^9/L$, and the decreased neutrophil count was $1.4 \times 10^9/L$. The event resolved after 4 days with no change in treatment.

In this medical reviewer's opinion, this single example of a significant adverse event is not related to treatment.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

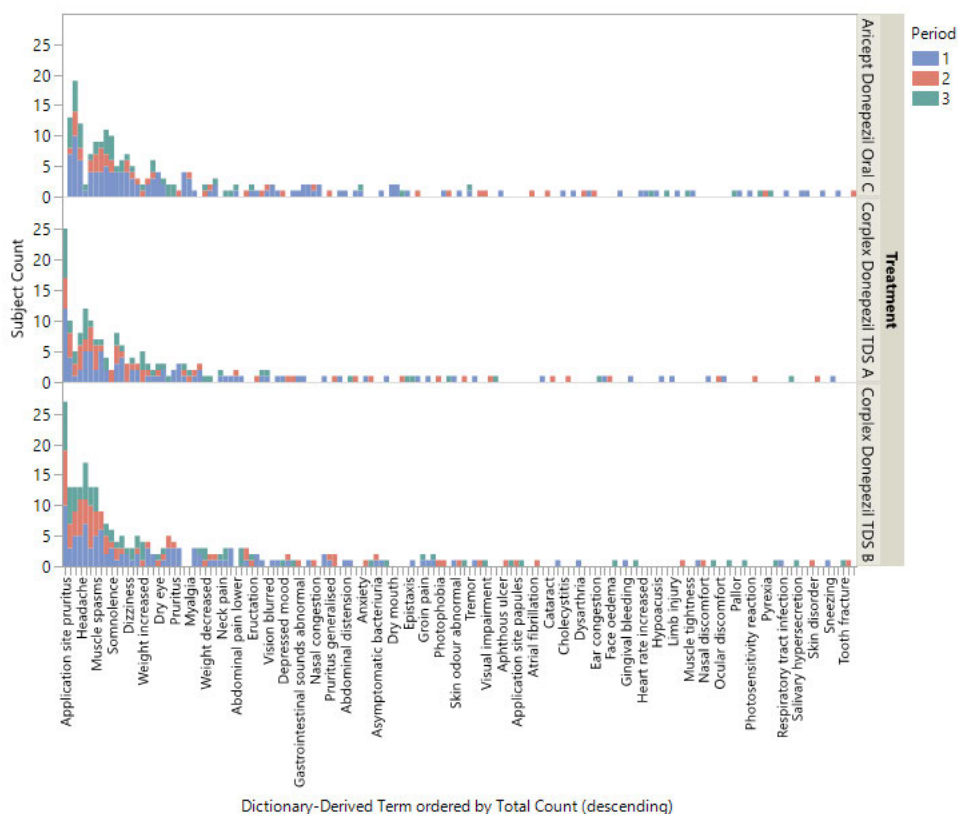
Overall TEAEs

There are only two IND studies (study 15086 [n = 60 enrolled] and study 16010 [n = 256 enrolled]) in which subjects were exposed to TDS or to oral donepezil in different treatment periods, thereby allowing a comparison of adverse event rates. These studies had very different designs, and hence the overall TEAE profile will be presented separately for each study below.

Study 15086

The following figure shows a display of TEAEs by treatment group.

Figure 1. TEAEs by Treatment, Study 15086



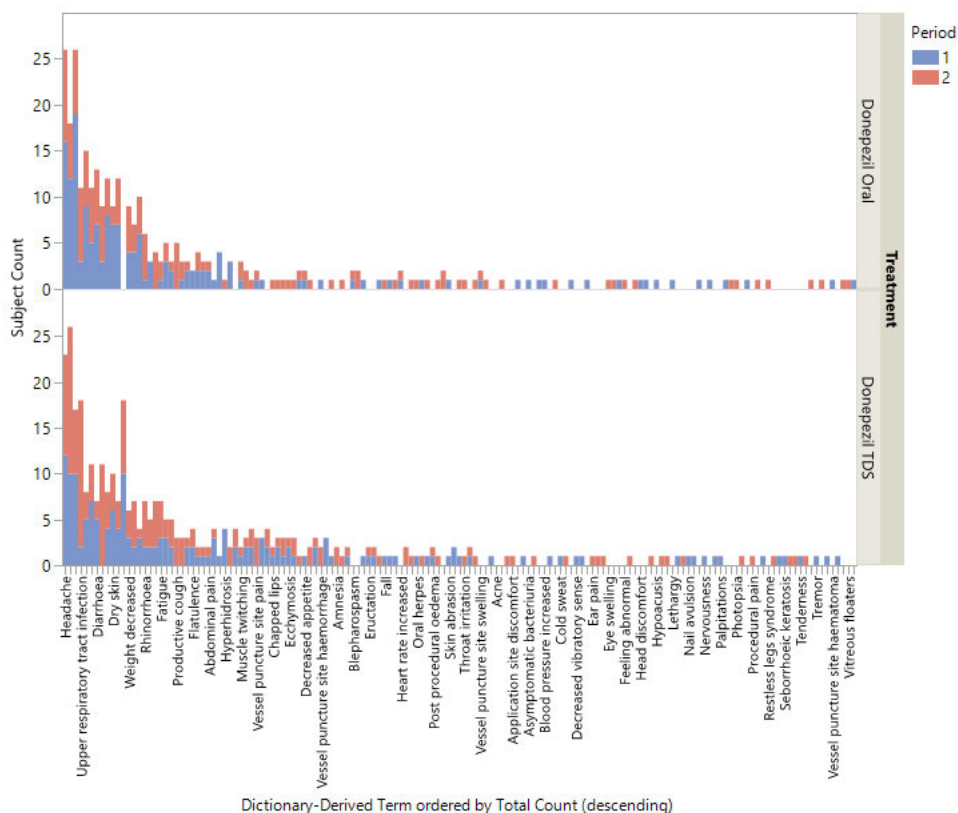
[Source: JMP Clinical, using SDTM and ADaM datasets from study 15086]

A visual comparison of TEAEs in the three groups (TDS A = 5mg/day; TDS B = 10mg/day; C = oral donepezil, 10mg daily) reveals that in general the rate of TEAEs in the TDS groups are similar to or less than the rates of corresponding TEAEs in the group receiving oral donepezil. However, the rates of application site events are necessarily higher in the group receiving TDS in study 15086 because donepezil was administered orally in this study.

Study 16010

Below is a figure of the TEAE profile by treatment group.

Figure 2. TEAEs by Treatment, Study 16010



[Source: JMP Clinical using study 16010 SDTM and ADaM datasets]

A visual comparison of TEAEs in the three groups (TDS = 10mg/day; oral donepezil = 10mg daily) reveals that in general the rate of TEAEs in the TDS group is similar to or less than the rates of corresponding TEAEs in the group receiving oral donepezil. As in study 15086, the rates of application site events are higher in the group receiving TDS in study 16010 because donepezil was administered orally in this study.

Adverse TEAEs of Special Interest in Studies 15086 and 16010

The following table displays selected gastrointestinal, musculoskeletal, and central nervous system adverse events of special interest by treatment, because these events are both commonly observed in patients who take donepezil, and also because these events are among those listed in the Adverse Reactions section of the Aricept label. The events that are listed in the Adverse Reactions section of the Aricept label are denoted “AR,” below.

Table 7: TEAE Profile of Studies 15086 and 16010

	Study 15086:	Study 16010:
--	--------------	--------------

	Rate (percent of subjects)		Rate (percent of subjects)	
	TDS (n = 56)	Donepezil (n = 58)	TDS (n = 85)	Donepezil (n = 82)
Nausea (AR)	23.6 %	32.8 %	20.0 %	31.7 %
Constipation	23.6	22.4	30.6	22.0
Diarrhea (AR)	12.7	19.0	8.2	15.9
Vomiting (AR)	3.6	10.3	9.4	14.6
Abnormal dreams	23.6	13.1	12.9	13.4
Nightmares	9.1	3.4	Not reported	Not reported
Insomnia (AR)	5.5	1.7	8.2	8.5
Fatigue (AR)	5.5	8.6	8.2	3.7
Anorexia (AR)	Not reported	Not reported	Not reported	Not reported
Dizziness	5.5	12.1	9.4	18.3
Somnolence	10.9	17.2	4.7	12.2
Muscle spasms (AR) ¹	23.6	15.5	8.2	14.6
Application site erythema	18.2	0	Not reported	Not reported
Application site pruritis	49.1	0	21.2	0
Application site pain	3.6	0	Not reported	Not reported

¹ The adverse reaction in the Aricept label is “muscle cramps.” In these studies, the events of “muscle spasms” are likely similar to muscle cramps; no verbatim event term of muscle cramps was reported in these studies.

[Source: Study CSRs]

Per the Aricept label, the most common Adverse Reactions (denoted as “AR,” above) in the pivotal approval studies include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. Regarding these Aricept ARs, the TEAE rates of nausea, vomiting and diarrhea are lower in the TDS-treated groups than in the donepezil-treated groups. Although the rates of insomnia, fatigue, and muscle spasms are higher in the TDS group than in the donepezil group in one of the two studies, the rates are lower in the other study. In other words, the overall event rates are similar when the two studies are considered together.

It is conceivable that application site reactions may be added to the adverse reactions label should TDS be approved, because these reactions are clearly related to the application of TDS. Below is a table that shows the application site events from all IND studies, when TDS (to deliver 5mg/day) was applied.

Table 8. TDS 5mg/day: Application Site Events

System Organ Class	Corplex Donepezil TDS 5 mg/day
Preferred Term	(N = 461)
	n (%)
Subjects with at Least One Application Site TEAE	75 (16.3%)
General disorders and administration site conditions	75 (16.3%)
Application site pruritus	67 (14.5%)
Application site pain	9 (2.0%)
Application site paraesthesia	3 (0.7%)
Application site papules	1 (0.2%)
Application site reaction	1 (0.2%)
Application site warmth	1 (0.2%)

N = number of subjects in the ISS Skin Tolerability Population, n = number of subjects with an event, Corplex Donepezil TDS 5 mg/day = patches with a 5 mg/day target dose (50 cm² and 53.5 cm² active drug area patches) applied to the back. All 5 mg/day patches are considered “Week 1” patches. In studies P-15086, P-15086 Sub-Study, P-16010, and P-16039, subjects received the 5 mg/day patches as the initial treatment during study periods in which donepezil patches were applied. In study P-16011, only the Week 1 5 mg/day patches were included.

Percentages were calculated as a function of the number of subjects in the Integrated Summary of Safety (ISS) Skin Tolerability Population.

[Source: Integrated Summary of Safety, Table 15-01]

Below is a table that shows the application site events from all IND studies, when TDS (to deliver 10mg/day) was applied.

Table 9. TDS 10mg/day: Application Site Events

System Organ Class Preferred Term	Corplex Donepezil TDS 10 mg/day (N = 178) n (%)
Subjects with at Least One Application Site TEAE	30 (16.9%)
General disorders and administration site conditions	30 (16.9%)
Application site pruritus	28 (15.7%)
Application site pain	2 (1.1%)
Application site discomfort	1 (0.6%)
Application site erythema	1 (0.6%)
Application site paraesthesia	1 (0.6%)

Abbreviations: N = number of subjects in the ISS Skin Tolerability Population, n = number of subjects with an event.

Corplex Donepezil TDS 10 mg/day = patches with 10 mg/day target dose (105 cm² and 107 cm² active drug area patches) applied to the back.

Note: Percentages were calculated as a function of the number of subjects in the ISS Skin Tolerability Population.

[Source: Integrated Summary of Safety, Table 15-01]

It is noteworthy that the rates of subjects with at least one application site TEAE are similar in the groups treated with TDS 5mg/day (16.3%) and TDS 10mg/day (16.9%). This similarity suggests that the reactions were due to the patch applications *per se*, irrespective of whether the patch delivered 5mg/day or 10mg/day of donepezil.

8.4.6. Laboratory Findings

In general, the blood clinical chemistry and hematology results by group did not differ between treatment groups at any point in time from Screening/Baseline values during treatment in any of the six IND studies. One exception is a subject who reported the significant adverse event of decreased neutrophil count, as described above in section 8.4.4.

The Aricept label contains no Warnings or Precautions regarding laboratory-associated events that are associated with Aricept use. Likewise, the Aricept label lists no laboratory-associated events that occur in a rate > 2%. It is therefore not surprising that the TDS laboratory-associated events did not differ during treatment from Screening/Baseline values.

8.4.7. Vital Signs

Across the six IND studies, the overall values for height, weight, temperature, and respiration did not exhibit any noteworthy group changes during treatments or between treatments.

Blood pressure elevations were reported in fifteen subjects in study 16011, ten of whom discontinued treatment due to the events. These events are discussed above (section 8.4.3), and the rates did not differ substantially from anticipated rates of reported hypertension based upon the Aricept label (i.e., 3%). There were five other subjects with reports of elevated blood pressure in the remaining five IND studies. The reported rates of these events were lower or similar to rates that would be anticipated based upon the reported rates for hypertension in the Aricept label.

Blood pressure elevations in subjects exposed to TDS were also reported in 1.6% of subjects in study 16012, in 4.3% of subjects in study 16039, and in 2.3% of subjects in the 15086 sub-study. These reported rates for TDS are similar to rates that would be anticipated based upon the Aricept label.

Heart rates exhibited no noteworthy group mean changes between treatments or during treatments. There were minor group mean changes from baseline in heart rate (< 4 beats per minute), consistent with anticipated donepezil-induced bradycardia.

Two subjects had atrial fibrillation: 1) Study 15086, subject P-15086-^{(b) (6)} (donepezil treatment); and 2) Study 16012, subject ^{(b) (6)} (TDS, 107cm² treatment, to deliver 10mg/day). The latter subject is described in greater detail under SAEs (section 8.4.2). As a general note, atrial fibrillation is relatively common in an older population, and this subject had documented cardiac irregularities before enrollment. It is not surprising that a single event of atrial fibrillation was reported in this TDS-treated older subject.

8.4.8. Electrocardiograms (ECGs)

Aside from the two subjects with atrial fibrillation cited above (section 8.4.7), there were no clinically noteworthy group changes during treatment in the IND studies. Minor group mean increases from baseline in PR, QRS, and RR intervals were noted, consistent with donepezil-induced bradycardia.

8.4.9. QT

QT intervals, corrected per the Fridericia method (i.e., QTcF), showed no absolute values > 500msec, and no changes from baseline > 60msec.

8.4.10. Immunogenicity

This section is not applicable for a transdermal delivery system.

8.5. Analysis of Submission-Specific Safety Issues

As cited in section 8.1, various safety or safety-related issues are relevant to a transdermal delivery system, and particularly for a product that is applied once weekly. These issues include patch adhesion during the week, skin irritation or skin sensitization produced by the system, the effects of heat or showering on the system, and any alterations in drug delivery if the patch is applied to body areas other than the back in an outpatient setting. In the sections below, these issues and the sponsor's approach to them are described in this order.

8.5.1. Patch Adhesion

Adhesion of TDS was evaluated in every IND study, but it was a key objective in study 15086 and in study 16010. For each study, the methods used to assess patch adhesion will be described, followed by the results of adhesion assessments. A significant feature to these studies is that they did not evaluate the potential separation of the patch layers expose the product (b) (4), as discussed further below (section 8.9.2)

Study 15086: Methods Used to Assess Patch Adhesion

Adhesion assessments were made at multiple time points (up to 17) each week during the 5-week patch application period. Adhesion was assessed in two ways, consistent with the FDA draft guidance (Food and Drug Administration 2016. *Assessing adhesion with transdermal delivery systems and topical patches for abbreviated new drug applications: draft guidance for industry*). First, the area of overall patch adhesion was measured, and the following scale was used to score overall patch adhesion.

Table 10. Overall Patch Adhesion Scale for Study 15086

Score	Percentage of TDS Adhered
0 =	≥ 90% adhered (essentially no lift off skin)
1 =	≥ 75% to < 90% adhered (some edges only lifting off skin)
2 =	≥ 50% to < 75% adhered (less than half the TDS lifting off skin)
3 =	< 50% adhered but did not detach (not detached, but more than half of the TDS lifting off skin without falling off)
4 =	patch completely detached (TDS detached, completely off skin)

[Source: Study 15086 CSR]

A second method was used to measure the area of adhesion of the drug delivery portion of

the patch, which covers less skin area than does the overall patch. At the same weekly time points that are described above, the area of adhesion of the drug delivery portion of the patch was measured, and the following scale was used to score adhesion of this drug delivery area.

Table 11. Adhesion of Drug Delivery Area for Study 15086

Score	Percentage of TDS Drug Delivery Area Adhered
0 =	100% adhered
1 =	≥ 90% adhered
2 =	≥ 80% adhered
3 =	≥ 70% adhered
4 =	≥ 60% adhered
5 =	≥ 50% adhered
6 =	0% to < 50% adhered

[Source: Study 15086 CSR]

The mean adhesion scores for each of these assessments was calculated, and the proportion of subjects with overall patch adhesion scores > 2 or drug delivery area adhesion scores > 5 was summarized.

Study 15086: Adhesion Results

The following table shows the mean adhesion scores of TDS (5mg/day lead-in for the first week, and then 10mg/day for the remaining four weeks).

Table 12. Overall Patch Adhesion Scores in Study 15086

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Week (TDS Dose)	Endpoint	Statistic	TDS A (N = 34)	TDS B (N = 35)
Week 1 (5 mg/day) TDS applied on Day 1	Mean Adhesion Score ^a	n	34	35
		Mean (SD)	0.09 (0.266)	0.18 (0.476)
		Min, Max	0.0, 1.0	0.0, 2.4
Week 2 (10 mg/day) TDS applied on Day 8	Mean Adhesion Score ^a	n	34	34
		Mean (SD)	0.08 (0.196)	0.07 (0.195)
		Min, Max	0.0, 0.9	0.0, 0.8
Week 3 (10 mg/day) TDS applied on Day 15	Mean Adhesion Score ^a	n	33	34
		Mean (SD)	0.09 (0.229)	0.16 (0.313)
		Min, Max	0.0, 1.0	0.0, 1.4
Week 4 (10 mg/day) TDS applied on Day 22	Mean Adhesion Score ^a	n	32	34
		Mean (SD)	0.07 (0.200)	0.11 (0.224)
		Min, Max	0.0, 0.9	0.0, 0.8
Week 5 (10 mg/day) TDS applied on Day 29	Mean Adhesion Score ^a	n	32	33
		Mean (SD)	0.06 (0.239)	0.09 (0.407)
		Min, Max	0.0, 1.1	0.0, 2.3
Weeks 2 to 5 (10 mg/day) Combined	Mean Adhesion Score ^a	n	131	135
		Mean (SD)	0.08 (0.214)	0.10 (0.294)
		Min, Max	0.0, 1.1	0.0, 2.3

Abbreviations: A = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 105 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; B = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 130 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; max = maximum; min = minimum; N = number of subjects with TDS in the Adhesion Population for each treatment; n = number of TDS with mean adhesion scores during the given time interval; TDS = transdermal delivery system.

Note: Adhesion Score: 0 = ≥ 90% adhered; 1 = ≥ 75% to < 90% adhered; 2 = ≥ 50% to < 75% adhered; 3 = < 50% adhered but not detached; 4 = 0% adhered.

a. Mean adhesion score is the average of the adhesion scores from 12 to 168 hours post application, where the adhesion score at a given post application time point for a given patch was defined as the highest post application adhesion score observed at or prior to the given time point.

[Source: Study 15086 CSR]

The following table depicts the proportion of subjects with an overall patch adhesion score > 2 (i.e., a score that indicates that < 50% of the patch adheres but it does not lift off of the skin).

Table 13. Proportion of Subjects with Overall Patch Adhesion Scores > 2 in Study 15086

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Week	Day TDS Applied	Target Dose	Statistic	Treatment A (N = 34)	Treatment B (N = 35)
Week 1	Day 1	5 mg/day	n	34	35
			m (%)	0	2 (5.7%)
Week 2	Day 8	10 mg/day	n	34	34
			m (%)	0	0
Week 3	Day 15	10 mg/day	n	33	34
			m (%)	0	0
Week 4	Day 22	10 mg/day	n	32	34
			m (%)	0	0
Week 5	Day 29	10 mg/day	n	32	33
			m (%)	0	1 (3.0%)

Abbreviations: A = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 105 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; B = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 130 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; m = number (%) of TDS with > 2 (< 50%) adhered; max = maximum; min = minimum; N = number of subjects with TDS in the Adhesion Population for each treatment; n = number of TDS with mean adhesion scores during the given time interval; TDS = transdermal delivery system.

Note: Adhesion Scale: 0 = ≥ 90% adhered; 1 = ≥ 75% to < 90% adhered; 2 = ≥ 50% to < 75% adhered; 3 = < 50% adhered but not detached; 4 = 0% adhered. The adhesion score at a given post application time point for a given patch was defined as the highest post application adhesion score observed at or prior to the given time point.

[Source: Study 15086 CSR]

Note that the adhesion scores for the overall patch showed good mean adhesion, with the highest (worst) score during any week of 0.18; this score indicates a mean adhesion of close to 90%. The proportion of subjects with a patch adhesion score > 2 was low, representing at most 2 subjects during any period.

The mean adhesion scores for the area of drug delivery are shown in the table below.

Table 14. Mean Adhesion of Drug Delivery Area in Study 15086

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Week (TDS Dose)	Endpoint	Statistic	Treatment A (N = 34)	Treatment B (N = 35)
Week 1 (5 mg/day) TDS applied on Day 1	Mean Adhesion Score ^a	n	34	35
		Mean (SD)	0.27 (0.546)	0.49 (0.894)
		Min, Max	0.0, 2.0	0.0, 4.9
	Maximum Adhesion Score ≤ 1 (≥ 90% adhered) ^b	n (%)	30 (88.2%)	27 (77.1%)
Week 2 (10 mg/day) TDS applied on Day 8	Mean Adhesion Score ^a	n	34	34
		Mean (SD)	0.30 (0.439)	0.46 (0.470)
		Min, Max	0.0, 1.4	0.0, 1.8
	Maximum Adhesion Score ≤ 1 (≥ 90% adhered) ^b	n (%)	30 (88.2%)	30 (88.2%)
Week 3 (10 mg/day) TDS applied on Day 15	Mean Adhesion Score ^a	n	33	34
		Mean (SD)	0.53 (0.466)	0.61 (0.640)
		Min, Max	0.0, 2.0	0.0, 2.8
	Maximum Adhesion Score ≤ 1 (≥ 90% adhered) ^b	n (%)	27 (81.8%)	25 (73.5%)
Week 4 (10 mg/day) TDS applied on Day 22	Mean Adhesion Score ^a	n	32	34
		Mean (SD)	0.27 (0.358)	0.55 (0.596)
		Min, Max	0.0, 1.4	0.0, 2.2
	Maximum Adhesion Score ≤ 1 (≥ 90% adhered) ^b	n (%)	28 (87.5%)	25 (73.5%)
Week 5 (10 mg/day) TDS applied on Day 29	Mean Adhesion Score ^a	n	32	33
		Mean (SD)	0.23 (0.467)	0.44 (0.643)
		Min, Max	0.0, 2.3	0.0, 3.4
	Maximum Adhesion Score ≤ 1 (≥ 90% adhered) ^b	n (%)	30 (93.8%)	30 (90.9%)
Weeks 2 to 5 (10 mg/day) Combined	Mean Adhesion Score ^a	n	131	135
		Mean (SD)	0.34 (0.446)	0.51 (0.588)
		Min, Max	0.0, 2.3	0.0, 3.4
	Maximum Adhesion Score ≤ 1 (≥ 90% adhered) ^b	n (%)	115 (87.8%)	110 (81.5%)

Abbreviations: A = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 105 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; B = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 130 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; max = maximum; min = minimum; N = number of subjects with TDS in the Adhesion Population for each treatment; n = number of TDS; TDS = transdermal delivery system.

[Source: Study 15086 CSR]

The proportion of subjects with a drug delivery area score > 5 (i.e., < 50% adherence) is illustrated below.

Table 15. Proportion of Subjects with Drug Delivery Score > 5 in Study 15086

Week	Day TDS Applied	Target Dose	Statistic	Treatment A (N = 34)	Treatment B (N = 35)
Week 1	Day 1	5 mg/day	n	34	35
			m (%)	0	2 (5.7%)
Week 2	Day 8	10 mg/day	n	34	34
			m (%)	0	0
Week 3	Day 15	10 mg/day	n	33	34
			m (%)	0	0
Week 4	Day 22	10 mg/day	n	32	34
			m (%)	0	0
Week 5	Day 29	10 mg/day	n	32	33
			m (%)	0	1 (3.0%)

Abbreviations: A = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 105 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; B = 5 mg/day donepezil (1 x 50 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 (Week 1) followed by 10 mg/day donepezil (1 x 130 cm² Corplex Donepezil TDS) applied weekly for 4 consecutive weeks from Week 2 to Week 5; m = number (%) of TDS with > 6 (< 50%) adhered; max = maximum; min = minimum; N = number of subjects with TDS in the Adhesion Population for each treatment; n = number of TDS with mean adhesion scores during the given time interval; TDS = transdermal delivery system.

Note: Extent of Adhesion Score for the drug delivery area: 0 = 100% adhered, 1 = ≥ 90% adhered, 2 = ≥ 80% adhered, 3 = ≥ 70% adhered, 4 = ≥ 60% adhered, 5 = ≥ 50% adhered, 6 = 0% to < 50% adhered.

[Source: Study 15086 CSR]

Note that the mean drug delivery area adhesion score is relatively low, with the highest (worst) mean score during any week of 0.61; this score indicates > 90% mean adherence of the drug delivery area. This score indicates somewhat poorer (though still acceptable) adhesion of the drug delivery area compared to the adhesion of the overall patch (0.18). The acceptable drug delivery area adhesion scores are also reflected by the proportion of subjects with a drug delivery area that showed a score > 5 (i.e., < 50% adherence); at most 2 subjects had this score during any period.

Study 16010: Methods Used to Assess Adhesion

The following 12-point numeric scale was used to measure both overall patch adhesion and adhesion of the drug delivery area in the 5-week treatment period, in which TDS was applied once weekly.

Table 16. Adhesion Assessment Scale for Study 16010

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Adhesion Measurement	Estimated Percent Adhered	Score
100%	100%	0
90% to < 100%	95%	1
80% to < 90%	85%	2
70% to < 80%	75%	3
60% to < 70%	65%	4
50% to < 60%	55%	5
40% to < 50%	45%	6
30% to < 40%	35%	7
20% to < 30%	25%	8
10% to < 20%	15%	9
> 0% to < 10%	5%	10
Detached	0%	11

[Source: Study 16010 CSR]

Study 16010: Adhesion Results

The overall patch adhesion scores and the proportion of subjects with an adhesion score > 5 (i.e., < 50% adherence) are presented in the table below.

Table 17. Overall Patch Adhesion Scores and Proportion of Subjects > 5 in Study 16010

APPEARS THIS WAY ON ORIGINAL

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Week TDS Applied (TDS Dose)	Endpoint	Statistic	Corplex Donepezil TDS (N = 85)
Week 1 (5 mg/day) TDS Applied on Day 1	Mean adhesion score ^a	n	85
		Mean (SD)	0.62 (0.531)
		Median	0.57
		Min, Max	0.0, 2.9
	Adhesion score > 5 (< 50% adhered) at any post-application time point	m (%) ^b	0 (0%)
	Detached patch (adhesion score = 11)	m (%) ^b	0 (0%)
Week 5 (10 mg/day) TDS Applied on Day 29	Mean adhesion score ^a	n	83
		Mean (SD)	0.94 (0.430)
		Median	0.86
		Min, Max	0.1, 2.9
	Adhesion score > 5 (< 50% adhered) at any post-application time point	m (%) ^b	1 (1.2%)
	Among patches with adhesion score > 5, time to adhesion score > 5 (days) ^c	Mean (SD)	7.0 (N/A)
	Detached patch (adhesion score = 11)	m (%) ^b	0 (0%)
Weeks 2 to 5 ^d (10 mg/day) Combined	Mean adhesion score ^a	n	338
		Mean (SD)	0.95 (0.511)
		Median	0.86
		Min, Max	0.0, 5.1
	Adhesion score > 5 (< 50% adhered) at any post-application time point ^b	m (%) ^b	4 (1.2%)
	Among patches with adhesion score > 5, time to adhesion score > 5 (days) ^c	Mean (SD)	5.9 (1.65)
		Median	6.5
		Min, Max	4, 7
	Detached patch (adhesion score = 11) ^b	m (%) ^b	0 (0%)

Abbreviations: Corplex Donepezil TDS = 53.5 cm² TDS (donepezil 5 mg/day) during Week 1 followed by 107 cm² TDS (donepezil 10 mg/day) during Weeks 2 to 5; m = number of patches in the adhesion population for the time period meeting the given criterion; N = number of subjects with patches in the adhesion population; n = number of patches in the adhesion population for the time period; N/A = not applicable; TDS = transdermal delivery system.

Note: Adhesion score (percent adhered): 0 = 100%; 1 = 90% to < 100%; 2 = 80% to < 90%; 3 = 70% to < 80%; 4 = 60% to < 70%; 5 = 50% to < 60%; 6 = 40% to < 50%; 7 = 30% to < 40%; 8 = 20% to < 30%; 9 = 10% to < 20%; 10 = > 0% to < 10%; 11 = complete detachment. The adhesion score at a post application time point for a given TDS was the highest post application score observed at or prior to the time point.

a. Mean adhesion score is the average of the adhesion scores from 12 to 168 hours post application.

b. Percent was calculated as (m/n)*100.

c. Number of days = date/time of first adhesion > 5 – date/time of application rounded to the nearest tenth of a day.

d. Includes all patches in the adhesion population applied during Weeks 2 to 5 combined.

[Source: Study 16010 CSR]

These results indicate > 95% mean adherence of the whole patch, and that at most 4 subjects (1.2%) had < 50% patch adherence during the study. When patch adherence was < 50%, this did not occur until a mean of 5.9 days into the 7-day application period of the patch.

The mean adhesion scores for the drug delivery area and the proportion of subjects with a drug delivery area adhesion score > 5 are shown below.

Table 18. Mean Adhesion of Drug Delivery Area and Proportion of Subjects > 5 in Study 16010

Week TDS Applied (TDS Dose)	Endpoint	Statistic	Corplex Donepezil TDS (N = 85)
Week 1 (5 mg/day) TDS Applied on Day 1	Mean adhesion score ^a	n	85
		Mean (SD)	0.31 (0.576)
		Median	0.0
		Min, Max	0.0, 2.9
	Adhesion score > 5 (< 50% adhered) at any post-application time point	m (%) ^b	0 (0%)
	Detached patch (adhesion score = 11)	m (%) ^b	0 (0%)
Week 5 (10 mg/day) TDS Applied on Day 29	Mean adhesion score ^a	n	83
		Mean (SD)	0.53 (0.513)
		Median	0.50
		Min, Max	0.1, 2.8
	Adhesion score > 5 (< 50% adhered) at any post-application time point	m (%) ^b	1 (1.2%)
	Among patches with adhesion score > 5, time to adhesion score > 5 (days) ^c	Mean (SD)	7.0 (N/A)
	Detached patch (adhesion score = 11)	m (%) ^b	0 (0%)
Weeks 2 to 5 ^d (10 mg/day) Combined	Mean adhesion score ^a	n	338
		Mean (SD)	0.60 (0.568)
		Median	0.50
		Min, Max	0.0, 4.5
	Adhesion score > 5 (< 50% adhered) at any post-application time point ^b	m (%) ^b	3 (0.9%)
	Among patches with adhesion score > 5, time to adhesion score > 5 (days) ^c	Mean (SD)	6.5 (0.5)
		Median	6.5
	Detached patch (adhesion score = 11) ^b	Min, Max	6, 7
		m (%) ^b	0 (%)

Abbreviations: Corplex Donepezil TDS = 53.5 cm² TDS (donepezil 5 mg/day) during Week 1 followed by 107 cm² TDS (donepezil 10 mg/day) during Weeks 2 to 5; m = number of patches in the adhesion population for the time period meeting the given criterion; N = number of subjects with patches in the adhesion population; n = number of patches in the adhesion population for the time period; N/A = not applicable; TDS = transdermal delivery system.

Note: Adhesion score (percent adhered): 0 = 100%; 1 = 90% to < 100%; 2 = 80% to < 90%; 3 = 70% to < 80%; 4 = 60% to < 70%; 5 = 50% to < 60%; 6 = 40% to < 50%; 7 = 30% to < 40%; 8 = 20% to < 30%; 9 = 10% to < 20%; 10 = > 0% to < 10%; 11 = complete detachment. The adhesion score at a post application time point for a given TDS was the highest post application score observed at or prior to the time point.

- Mean adhesion score is the average of the adhesion scores from 12 to 168 hours post application.
- Percent was calculated as (m/n)*100.
- Number of days = date/time of first adhesion > 5 – date/time of application rounded to the nearest tenth of a day.
- Includes all patches in the adhesion population applied during Weeks 2 to 5 combined.

[Source: Study 16010 CSR]

The data for the combined patch scores from weeks 2 – 5 (i.e., the period in which TDS delivered 10mg/day) indicate a mean drug delivery area adhesion score of 0.6, or > 95% mean adhesion. Only 0.9% of subjects had patches in which adhesion of the drug delivery area was < 50%, and the mean time elapsed before adherence fell to < 50% was nearly 7 days (i.e., the end of each weekly wearing period).

8.5.2. Skin Irritation and Sensitization

A skin irritation and sensitization study was conducted (study 16011). In this study, 256 subjects were randomized to a three-week induction phase during which they had weekly applications of TDS (5mg/day) to the same site on either the right or left side of the back, and of vehicle-containing patches to the other side of the back. Skin irritation was assessed following patch removal at the end of each week using a Combined Irritation score, calculated as the sum of the scores from the Dermal Response scale (table below) and the Other Effects scale (table further below). The scoring method used for the Other Effects scale was Method 1 for FDA purposes, and Method 2 for EMA purposes. The mean Combined Irritation score was then calculated for the entire three-week period.

Table 19. Dermal Response Scale for Study 16011

Description	Numeric Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; minimal edema; or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

[Source: Study 16011 CSR]

Table 20. Other Effects Scale for Study 16011

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Observation	Score (Method 1) (Numeric Equivalent)	Score (Method 2) (Numeric Equivalent)
None observed	(0)	0
Slightly glazed appearance	A (0)	1
Marked glazed appearance	B (1)	2
Glazing with peeling and cracking	C (2)	3
Glazing with fissures	F (3)	4
Film of dried serous exudate covering all or part of the application site	G (3)	4
Small petechial erosions and/or scabs	H (3)	4

[Source: Study 16011 CSR]

Skin Sensitization was then assessed as follows. Fourteen days after this three-week induction phase, a challenge phase was conducted in which TDS and a vehicle-containing patch were applied to naïve site on opposite sides of the back for 48 hours, and the Combined Irritation score was assessed 72 hours after patch removal. All subjects with a Combined Irritation score that was both ≥ 2 during this challenge phase and also higher than the maximum score during the induction phase were eligible for a re-challenge phase to evaluate potential sensitization. The re-challenge phase occurred four weeks after the challenge phase. During the re-challenge phase, patches were applied to a naïve site on the back for 48 hours, and the Combined Irritation score was assessed 48 - 72 hours after patch removal. Combined Irritation scores ≥ 2 were considered to represent potential sensitization.

Skin Irritability in Study 16011

The following table shows the Combined Irritation scores during the three-week induction phase.

Table 21. Combined Irritation Scores During Induction Phase in Study 16011

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarly (donepezil transdermal system) for AD

Scheduled Time Point	n ^b	Corplex TDS Combined Skin Irritation Score ^a (N = 585) ^b							n ^b	Vehicle TDS Combined Skin Irritation Score ^a (N = 582) ^b						
		0	1	2	3	4	5	> 5		0	1	2	3	4	5	> 5
Induction Phase																
Day 8, 30 min post TDS removal	195	154 (79.0%)	35 (17.9%)	4 (2.1%)	0	2 (1.0%)	0	0	194	153 (78.9%)	33 (17.0%)	8 (4.1%)	0	0	0	0
Day 15, 30 min post TDS removal	194	144 (74.2%)	35 (18.0%)	12 (6.2%)	0	2 (1.0%)	0	1 (0.5%)	193	170 (88.1%)	17 (8.8%)	6 (3.1%)	0	0	0	0
Day 22, 30 min post TDS removal	195	76 (39.0%)	72 (36.9%)	39 (20.0%)	3 (1.5%)	2 (1.0%)	0	3 (1.5%)	193	164 (85.0%)	25 (13.0%)	4 (2.1%)	0	0	0	0
Maximum score post TDS removal	195	64 (32.8%)	81 (41.5%)	41 (21.0%)	3 (1.5%)	3 (1.5%)	0	3 (1.5%)	194	131 (67.5%)	51 (26.3%)	12 (6.2%)	0	0	0	0

Abbreviations: TDS = transdermal delivery system

^a The Combined Irritation score at each skin assessment time point for each patch (Corplex Donepezil TDS or Vehicle TDS) is defined as the sum of the Dermal Response and Other Effects scale scores. Dermal Response scale scores ranged from 0 = no evidence of irritation to 7 = strong reaction spreading beyond test (i.e., application) site. Scoring Method 1 was used to score the Other Effects scale: 0 = none observed or slight glazed appearance; 1 = marked glazed appearance; 2 = glazing with peeling and cracking; 3 = glazing with fissures, film of dried serous exudates covering all or part of the patch site, or small petechial erosions and/or scabs. The following adjustments were made to the Dermal Response and Other Effects scale scores prior to computing the Combined Irritation score:

- Scheduled 30-minute post TDS removal skin assessments made more than 1 hour after TDS removal were set to missing.
- Skin assessment scores made after a patch was moved or removed due to unacceptable skin irritation were imputed by carrying forward the last observation made prior to moving or removing the patch.

^b N is the number of patches in the Per Protocol Skin Irritation Population for each treatment. The n for each treatment at each post TDS removal time point is the number of patches with skin irritation assessments made within 1 hour of TDS removal. The number (%) of patches with the indicated Combined Irritation scores at each time point are shown, where percentages were calculated based on the n for each treatment at the given time point.

[Source: Study 16011 CSR]

Note that Combined Irritation scores were shifted to higher (worse) values in the TDS group compared to the Vehicle group. The mean Combined irritation score following TDS application was 0.55, and the score following application of the vehicle-containing patch was 0.19 (data not shown). This indicates that although relatively minor, there was greater skin irritation following application of TDS than following application of vehicle-containing patches.

There was no clear effect of age, gender, or ethnicity on the Combined Irritation scores during the induction phase. However, it is possible that the TDS was better tolerated by subjects over 65 years of age, by female subjects, and by subjects with ethnicity that was not Hispanic or Latino. These data are shown in the following table.

Table 22. Effects of Age, Gender, and Ethnicity on Combined Irritation Scores in Study 16011

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Maximum Combined Irritation Score During Induction Phase ^a	n ^b	Corplex TDS (N = 585) ^b							n ^b	Vehicle TDS (N = 582) ^b						
		0	1	2	3	4	5	>5		0	1	2	3	4	5	>5
Age Category																
< 50 years	74	19 (25.7%)	37 (50.0%)	16 (21.6%)	1 (1.4%)	1 (1.4%)	0	0	76	49 (64.5%)	21 (27.6%)	6 (7.9%)	0	0	0	0
50 - < 65 years	91	31 (34.1%)	32 (35.2%)	21 (23.1%)	2 (2.2%)	2 (2.2%)	0	3 (3.3%)	88	59 (67.0%)	25 (28.4%)	4 (4.5%)	0	0	0	0
≥ 65 years	30	14 (46.7%)	12 (40.0%)	4 (13.3%)	0	0	0	0	30	23 (76.7%)	5 (16.7%)	2 (6.7%)	0	0	0	0
Gender																
Male	77	19 (24.7%)	35 (45.5%)	16 (20.8%)	2 (2.6%)	3 (3.9%)	0	2 (2.6%)	75	48 (64.0%)	18 (24.0%)	9 (12.0%)	0	0	0	0
Female	118	45 (38.1%)	46 (39.0%)	25 (21.2%)	1 (0.8%)	0	0	1 (0.8%)	119	83 (69.7%)	33 (27.7%)	3 (2.5%)	0	0	0	0
Ethnicity																
Hispanic or Latino	61	26 (42.6%)	21 (34.4%)	14 (23.0%)	0	0	0	0	64	45 (70.3%)	16 (25.0%)	3 (4.7%)	0	0	0	0
Not Hispanic or Latino	134	38 (28.4%)	60 (44.8%)	27 (20.1%)	3 (2.2%)	3 (2.2%)	0	3 (2.2%)	130	86 (66.2%)	35 (26.9%)	9 (6.9%)	0	0	0	0

Abbreviations: TDS = transdermal delivery system

^a The Combined Irritation score at each skin assessment time point for each patch (Corplex Donepezil TDS or Vehicle TDS) is defined as the sum of the Dermal Response and Other Effects scale scores. Dermal Response scale scores ranged from 0 = no evidence of irritation to 7 = strong reaction spreading beyond test (i.e., application) site. Scoring Method 1 was used to score the Other Effects scale: 0 = none observed or slight glazed appearance; 1 = marked glazed appearance; 2 = glazing with peeling and cracking; 3 = glazing with fissures, film of dried serous exudates covering all or part of the patch site, or small petechial erosions and/or scabs. The following adjustments were made to the Dermal Response and Other Effects scale scores prior to computing the Combined Irritation score:

- Scheduled 30-minute post TDS removal skin assessments made more than 1 hour after TDS removal were set to missing.
- Skin assessment scores made after a patch was moved or removed due to unacceptable skin irritation were imputed by carrying forward the last observation made prior to moving or removing the patch.

^b N is the number of patches in the Per Protocol Skin Irritation Population for each treatment. The n for each treatment is the number of patches with skin irritation assessments made within 1 hour of TDS removal. The number (%) of patches with the indicated Combined Irritation scores are shown, where percentages were calculated based on the n for each treatment.

[Source: Study 16011 CSR]

As shown in Table 21, 47 subjects were eligible for the re-challenge phase following application of TDS (i.e., Combined Irritation scores ≥ 2), whereas only 12 subjects were eligible for the re-challenge phase following application of the vehicle-containing patch.

Potential Sensitization in Study 16011

When re-challenged at a naïve site on their back, 4 subjects showed potential sensitization following application of TDS, and no subject showed potential sensitization following application of vehicle. These results appear to indicate that there is a relatively small potential for sensitization from application of TDS.

8.5.3. Effect of Heat on PK Parameters, Combined Irritation Scores, and Adhesion

Study 16039 evaluated the effect of applying a heating pad on three occasions (days 2, 4, and 7) to the application site of TDS (5mg/day) in 24 subjects in a two-way crossover. The C_{max} and $AUC_{0-168 \text{ hrs}}$ were similar in the presence or absence of heat as depicted below.

Table 23. Plasma PK Parameters for Donepezil in the Presence or Absence of Heat in Study 16039

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Treatment	n	Adjusted Geometric Mean ^a	Comparison	Adjusted GMR	P-value	90% Confidence Interval
AUC₀₋₁₆₈ (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				

[Source: Study 16039 CSR]

There was no noteworthy difference in the Combined Irritation scores between subjects with heat application and subjects with no heat application, as shown by the following table.

Table 24. Combined Irritation Scores in the Presence and Absence of Heat in Study 16039

	Corplex Donepezil TDS + Applied Heat (N = 22) n/m (%)	Corplex Donepezil TDS + No Applied Heat (N = 22) n/m (%)	Corplex Donepezil TDS Extension Period (N = 6) n/m (%)
Irritation Event			
Combined Irritation Score ^a ≥ 3 at 0.5 hours post TDS Removal	0/22	1/22 (4.5%)	0/6
Combined Irritation Score ≥ 3 at any point from 0.5 hours through 72 hours post TDS Removal ^b	0/22	1/22 (4.5%)	0/6
Removed due to Excessive Irritation	0/22	1/22 (4.5%)	0/6

Abbreviations: Corplex Donepezil TDS + Applied Heat = 5 mg per day donepezil (53.5 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1+ heating pad for three 2-hour Heat Sessions over a 7-hour Heat Interval on Days 2, 4, and 7. Corplex Donepezil TDS + No Applied Heat = 5 mg per day donepezil (53.5 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 + no heating pad, Extension Period = Single 2-day application of the 5 mg per day donepezil (53.5 cm² Corplex Donepezil TDS), m = number of patches in the skin tolerability population, N = number of subjects in the skin tolerability population, n = the number of TDS in the skin tolerability population at the time point, TDS = transdermal delivery system.

Note: Combined Irritation Score is defined as the sum of the Dermal Response score and Other Effects score at each time point per TDS.

Note: Percentages are calculated based on the number of Corplex Donepezil TDS (m).

Note: If a TDS was moved or removed due to excessive irritation, it was included at the scheduled postremoval time points using last observation carried forward.

a. Combined Irritation Score is defined as the sum of the Dermal Response score and Other Effects score at each time point per TDS.

b. Combined Irritation Score ≥ 3 at 0.5 hours, 24 hours, 48 hours, or 72 hours post Corplex Donepezil TDS removal.

[Source: Study 16039 CSR]

Adhesion scores were assessed using the same scoring methods that were used in study 16010, as described further above. TDS adhesion parameters were similar in the presence and absence of heat, as shown by the following table. Note the nearly identical mean adhesion scores (0.70 without heat vs. 0.76 with heat), and an identical proportion of subjects with adhesion scores > 5 (9.1%) in each treatment arm.

Table 25. Adhesion as a Function of Heat in Study 16039

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarly (donepezil transdermal system) for AD

Treatment	Endpoint		Corplex Donepezil TDS
Corplex Donepezil TDS + Applied Heat (N = 22)	Mean Adhesion Score ^a	n	22
		Mean (SD)	0.76 (0.302)
		Median	0.86
		Min, Max	0.2, 1.6
	Number of Corplex Donepezil TDS with adhesion score > 5 (< 50% adhered) ^b	n (%)	2 (9.1%)
	Among Corplex Donepezil TDS with adhesion score > 5, Time to Adhesion Score > 5 (days) [3]	Mean (SD)	1.15 (0.212)
		Median	1.15
Corplex Donepezil TDS + No Applied Heat (N = 22)	Mean Adhesion Score ^a	n	22
		Mean (SD)	0.70 (0.311)
		Median	0.71
		Min, Max	0.1, 1.3
	Number of Corplex Donepezil TDS with adhesion score > 5 (< 50% adhered) ^b	n (%)	2 (9.1%)
	Among Corplex Donepezil TDS with adhesion score > 5, Time to Adhesion Score > 5 (days) ^c	Mean (SD)	4.75 (1.061)
		Median	4.75
	Number of Corplex Donepezil TDS Taped	n (%)	14 (63.6%)
	Number of Corplex Donepezil TDS detached (adhesion score = 11) ^b	n (%)	1 (4.5%)

Abbreviations: Corplex Donepezil TDS + Applied Heat = 5 mg per day donepezil (53.5 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 + heating pad for three 2-hour Heat Sessions over a 7-hour Heat Interval on Days 2, 4, and 7, Corplex Donepezil TDS + No Applied Heat = 5 mg per day donepezil (53.5 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 + no heating pad, Min = minimum, Max = maximum, N = number of subjects in the adhesion population, n = the number of Corplex Donepezil TDS in the adhesion population, SD = Standard deviation, TDS = transdermal delivery system.

Note: Adhesion Score (percent adhered): 0 = 100% adhered, 1 = 90% to < 100% adhered, 2 = 80% to < 90% adhered, 3 = 70% to < 80% adhered, 4 = 60% to < 70% adhered, 5 = 50% to < 60% adhered, 6 = 40% to < 50% adhered, 7 = 30% to < 40% adhered, 8 = 20% to < 30% adhered, 9 = 10% to < 20% adhered, 10 = > 0% to < 10% adhered, 11 = detached. The adhesion score at a post application time point for a given TDS was the highest post application score observed at or prior to the endpoint. If a Corplex Donepezil TDS became completely detached before the end of the 7-day Corplex Donepezil TDS application period, a score of 11 (complete patch detachment) was carried forward for all subsequent TDS assessments.

a. Mean adhesion score is the average of the adhesion scores from 12 hour post application to 168 hours post application.

b. Numerator based on any post application score meeting the criteria. Denominator is based on the number of patches applied for the period.

[Source: Study 16039 CSR]

8.5.4. PK Parameters, Combined Irritation Scores, and Adhesion as a Function of Body Site Application

Study 16012 tested the application of TDS (10mg/day) to the back, thigh, or buttock in 66 subjects using a three-way crossover design. Adhesion was assessed using the methods described further above for study 16010.

Plasma PK parameters (C_{max} and AUC_{0-inf}) for donepezil were relatively similar irrespective of the anatomic site of application per the following table. Although these parameters were lower for TDS application on the thigh than on the back, and higher for TDS application on the buttock than on the back, both sets of parameters appear to have met bioequivalence criteria.

Table 26. Plasma PK Parameters for Donepezil as a Function of Application Site in Study 16012

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

AUC_{inf} (h*ng/mL)					
TDS Thigh	56	4666.824	TDS Thigh/TDS Back	0.806	(0.744, 0.873)
TDS Back	57	5789.022			
TDS Buttock	57	7118.594	TDS Buttock/TDS Back	1.230	(1.136, 1.331)
TDS Back	57	5789.022			
C_{max} (ng/mL)					
TDS Thigh	56	21.514	TDS Thigh/TDS Back	0.779	(0.719, 0.844)
TDS Back	57	27.631			
TDS Buttock	57	33.562	TDS Buttock/TDS Back	1.215	(1.121, 1.316)
TDS Back	57	27.631			

Abbreviations: AUC₀₋₁₆₈ = Area under the plasma concentration-time curve during a 1-week application time from 0 to 168 hours, AUC_{inf} = AUC from Time 0 to infinity, C_{max} = maximum observed concentration, GMR = geometric mean ratio, TDS Back = Back application of Corplex Donepezil TDS = 10 mg/day Donepezil (1 × 107 cm² 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 cm² 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 cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days, TDS = transdermal delivery system.

Note: Bioequivalence criteria are met if the 90% CI of the adjusted geometric mean ratio for AUC₀₋₁₆₈, AUC_{inf}, and C_{max} are completely within the interval 0.8 to 1.25.

Note: n refers to the number of subjects included in the analysis.

[Source: Study 16012 CSR]

As depicted below, the mean adhesion score of the drug delivery area was somewhat better on the buttock (mean score of 0.16) and thigh (mean score of 0.41) than on the back (mean score of 0.70). However, the numbers of subjects with adhesion scores > 5 was negligible irrespective of the anatomic site of application.

Table 27. Mean Adhesion Scores for Drug Delivery Area as a Function of Application Site in Study 16012

APPEARS THIS WAY ON ORIGINAL

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

Endpoint	Statistics	Corplex Donepezil TDS Back N = 60	Corplex Donepezil TDS Thigh N = 61	Corplex Donepezil TDS Buttock N = 62
Mean Adhesion Score ^a	n	60	61	62
	Mean (SD)	0.70 (0.857)	0.41 (0.760)	0.16 (0.293)
	Median	0.57	0.00	0.00
	Min, Max	0.0, 5.2	0.0, 5.0	0.0, 1.0
Number of Corplex Donepezil TDS with Adhesion Score > 5 (< 50% adhered) ^b	n (%)	1 (1.7%)	1 (1.6%)	0
Among Corplex Donepezil TDS with Adhesion Score > 5, Time to Adhesion Score > 5 (days) ^c	Mean (SD)	3.51 (N/A)	3.99 (N/A)	---
	Median	3.51	3.99	---
Number of Subjects with Both a Back and the Test Location Mean Adhesion Score	M	---	59	59
Subjects with a Test Location Mean Adhesion Score > the Corresponding Back Mean Adhesion Score by 3 or More ^d	m (%)	---	1 (1.7%)	0
Subjects with a Back Mean Adhesion Score > the Corresponding Test Location Mean Adhesion Score by 3 or More ^d	m (%)	---	1 (1.7%)	1 (1.7%)

Abbreviations: Corplex Donepezil TDS = 10 mg/day donepezil (1 × 10⁷ cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days; M = number of subjects with both a TDS Back and the test location mean adhesion score; m = number of subjects; N = number of TDS in the adhesion population in each application site; n = number of Corplex Donepezil TDS; SD = standard deviation; TDS = transdermal delivery system.

Note: Adhesion Score: 0 = 100% adhered; 1 = 90% to < 100% adhered; 2 = 80% to < 90% adhered; 3 = 70% to < 80% adhered; 4 = 60% to < 70% adhered; 5 = 50% to < 60% adhered; 6 = 40% to < 50% adhered; 7 = 30% to < 40% adhered; 8 = 20% to < 30% adhered; 9 = 10% to < 20% adhered; 10 = > 0% to < 10% adhered; 11 = detached. The adhesion score at a post application time point for a given Corplex Donepezil TDS is the highest post application score observed at or prior to the time point.

a: Mean adhesion score is the average of the adhesion scores from 12 hours post application to 168 hours post application.

b: Numerator is the number of Corplex Donepezil TDS with one or more post application adhesion scores > 5. Denominator is based on the number of Corplex Donepezil TDS in the adhesion population.

c: Number of days = [date/time of first adhesion score > 5 – date/time of application + 1 hour]/24.

d: Numerator is based on the number of subjects with mean adhesion scores meeting the criterion. Denominator is based on the number of subjects with both a TDS Back and the test location mean adhesion score.

[Source: Study 16012 CSR]

There was no difference in Combined Irritation scores irrespective of the anatomic site of TDS application, as demonstrated below.

Table 28. Combined Irritation Scores as a Function of Application Site in Study 16012

Combined Irritation Endpoint ^b	Corplex Donepezil TDS Back ^a (N = 59)	Corplex Donepezil TDS Thigh ^a (N = 61)	Corplex Donepezil TDS Buttock ^a (N = 62)
M	59	61	62
Combined irritation score ≥ 3 at 30 minutes post TDS removal	0	0	0
Combined irritation score ≥ 3 at 24 hours post TDS removal	0	0	0
Combined irritation score ≥ 3 at 48 hours post TDS removal	0	0	0
Combined irritation score ≥ 3 at 72 hours post TDS removal	0	0	0
Combined irritation score ≥ 3 at any time point from 30 minutes through 72 hours post TDS removal	0	0	0
Removed due to an excessive degree of irritation	0	0	0

Abbreviations: M = number of Corplex Donepezil TDS in the population in each application site; N = number of subjects in the population in each application site; TDS = transdermal delivery system.

Note: Percentages are calculated based on the number of Corplex Donepezil TDS in the skin tolerability population per application site.

Note: If a Corplex Donepezil TDS was removed due to an unacceptable degree of irritation, it was included at the scheduled post removal time points using last observation carried forward.

a: Corplex Donepezil TDS = 10 mg/ day donepezil (1 × 10⁷ cm² Corplex Donepezil TDS) applied at Hour 0 on Day 1 for 7 days.

b: Combined Irritation Score is defined as the sum of the Dermal Response score and Other Effects score at each time point per Corplex Donepezil TDS.

[Source: Study 16012 CSR]

8.6. Safety Analyses by Demographic Subgroups

Demographic subgroups in study 16011 were evaluated to determine differences, if any, in the skin irritation and sensitization. As described in section 8.5.2, the Combined Irritation score was assessed as a function of gender, ethnicity, and age. No clear differences were observed in combined irritation scores as a function of these groups, as shown in the table below.

Table 29. Combined Irritation Scores as a Function of Age, Gender, and Ethnicity in Study 16011

Maximum Combined Irritation Score During Induction Phase ^a	n ^b	Corplex TDS (N = 709) ^b							n ^b	Vehicle TDS (N = 702) ^b						
		0	1	2	3	4	5	>5		0	1	2	3	4	5	>5
Age Category																
< 50 years	89	21 (23.6%)	41 (46.1%)	25 (28.1%)	1 (1.1%)	1 (1.1%)	0	0	89	55 (61.8%)	27 (30.3%)	7 (7.9%)	0	0	0	0
50 - < 65 years	109	33 (30.3%)	41 (37.6%)	28 (25.7%)	2 (1.8%)	2 (1.8%)	0	3 (2.8%)	108	71 (65.7%)	31 (28.7%)	6 (5.6%)	0	0	0	0
≥ 65 years	38	16 (42.1%)	15 (39.5%)	7 (18.4%)	0	0	0	0	37	27 (73.0%)	8 (21.6%)	2 (5.4%)	0	0	0	0
Gender																
Male	93	22 (23.7%)	41 (44.1%)	23 (24.7%)	2 (2.2%)	3 (3.2%)	0	2 (2.2%)	91	58 (63.7%)	21 (23.1%)	12 (13.2%)	0	0	0	0
Female	143	48 (33.6%)	56 (39.2%)	37 (25.9%)	1 (0.7%)	0	0	1 (0.7%)	143	95 (66.4%)	45 (31.5%)	3 (2.1%)	0	0	0	0
Ethnicity																
Hispanic or Latino	69	27 (39.1%)	22 (31.9%)	20 (29.0%)	0	0	0	0	69	48 (69.6%)	18 (26.1%)	3 (4.3%)	0	0	0	0
Not Hispanic or Latino	167	43 (25.7%)	75 (44.9%)	40 (24.0%)	3 (1.8%)	3 (1.8%)	0	3 (1.8%)	165	105 (63.6%)	48 (29.1%)	12 (7.3%)	0	0	0	0

Abbreviations: TDS = transdermal delivery system

^a The Combined Irritation score at each skin assessment time point for each patch (Corplex Donepezil TDS or Vehicle TDS) is defined as the sum of the Dermal Response and Other Effects scale scores. Dermal Response scale scores ranged from 0 = no evidence of irritation to 7 = strong reaction spreading beyond test (i.e., application) site. Scoring Method 1 was used to score the Other Effects scale: 0 = none observed or slight glazed appearance; 1 = marked glazed appearance; 2 = glazing with peeling and cracking; 3 = glazing with fissures, film of dried serous exudates covering all or part of the patch site, or small petechial erosions and/or scabs. The following adjustments were made to the Dermal Response and Other Effects scale scores prior to computing the Combined Irritation score:

- Scheduled 30-minute post TDS removal skin assessments made more than 1 hour after TDS removal were set to missing.
- Skin assessment scores made after a patch was moved or removed due to unacceptable skin irritation were imputed by carrying forward the last observation made prior to moving or removing the patch.

^b N is the number of patches in the Sensitivity Analysis Skin Irritation Population for each treatment. The n for each treatment is the number of patches with skin irritation assessments made within 1 hour of TDS removal. The number (%) of patches with the indicated Combined Irritation scores are shown, where percentages were calculated based on the n for each treatment.

[Source: Study 16011 CSR]

8.7. Specific Safety Studies/Clinical Trials

Sections above described special safety studies that were conducted to evaluate TDS adhesion (sec. 8.5.1), skin irritation and sensitization (sec. 8.5.2), the effect of heat on adhesion and plasma PK of donepezil (section 8.5.3), and the effect of TDS body application site on adhesion, Combined Irritation scores, and plasma PK parameters of donepezil (sec. 8.5.4).

There were no other special safety studies. The results of safety evaluations for each relevant

study are presented in sections further above.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity studies have been conducted.

8.8.2. Human Reproduction and Pregnancy

No pregnancies occurred during these studies. Because TDS is intended to be used in people with Alzheimer's disease, women of childbearing potential will be rare in the outpatient population that is treated with TDS.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric subjects have not been evaluated in these studies. Because TDS is intended to be used in people with AD, a pediatric indication is not warranted.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Donepezil does not have drug abuse potential, and it is not known to produce withdrawal or rebound effects.

Overdoses with donepezil can produce symptoms of exaggerated pharmacology that can be anticipated for an acetylcholinesterase inhibitor. Signs of a donepezil overdose could include bradycardia, heart block, hypotension, vomiting, diarrhea, bladder outflow obstruction, seizures, bronchoconstriction that can be symptomatic in patients with asthma or COPD, and muscle weakness. Overdoses can be managed using anticholinergic agents such as atropine.

8.9. Safety in the Post-market Setting

8.9.1. Safety Concerns Identified Through Post-market Experience

Per the Aricept label, post-marketing adverse reactions that have been reported include abdominal pain, agitation, aggression, cholecystitis, confusion, convulsions, hallucinations, heart block, hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, rash, rhabdomyolysis, QTc prolongation and torsade de pointes.

8.9.2. Expectations on Safety in the Post-market Setting

In a direct comparison of TEAEs following application of TDS vs. oral donepezil (per the Aricept label), the distribution of TEAEs reported with TDS was similar in profile, and the reporting rate of anticipated events (e.g., nausea, dizziness, muscle spasms) with TDS was typically lower or similar to rates with oral donepezil (section 8.4.5), with one exception that is described later in this section. Based purely upon these results from the IND studies, it could be anticipated that use of TDS in clinical settings should result in a similar adverse event profile, at lower or similar rates to those that occur with currently approved oral donepezil. However, see the discussion about Product Quality in the third paragraph below, regarding the potential separation of patch layers to expose the product (b) (4).

One additional adverse event grouping that can be anticipated specifically for TDS consists of a variety of application site reactions. Skin irritation was observed regularly in the trials conducted by the sponsor, but combined irritation scores were low, and the events were transient and reversible following patch removal. Potential skin sensitization was observed infrequently when it was evaluated (approximately 1.6%). Hence, application site reactions are manageable, and if needed TDS could be discontinued in individuals who do not tolerate application site reactions.

However, the Product Quality of TDS has been found to be unacceptable due to the relative ease with which (b) (4). These issues are described in depth in the review submitted by Product Quality and other disciplines. Briefly and as described in a number of sections of this review, the patch (b) (4) can be separated (b) (4) with relative ease. If separation occurs when the patient is wearing the patch, significant alterations in dosing may occur. If separation occurs when the patch is being applied or being removed, both patient and caregiver may be exposed to donepezil if they touch the product (b) (4). These potential safety risks were not reported in the studies submitted with this NDA. However, in post-marketing use, these potential safety risks are unacceptable, and they are the basis for my recommendation that this product not be approved and that a CR be issued.

8.9.3. Additional Safety Issues From Other Disciplines

As described above and in other sections, there is a serious product quality issue that is reviewed separately by other disciplines. The issue, separation of the patch layers, could potentially result in incorrect dosing in patients in whom the patch separation may occur, and/or in direct exposure to donepezil if the separated product delivery matrix is touched by the patient or the caregiver. This serious safety concern is the basis for my recommendation

that the product is not approved and that a CR is issued.

8.10. Integrated Assessment of Safety

Donepezil has a well-known safety profile, and it is generally well-tolerated in the Alzheimer's disease population. Common adverse events include gastrointestinal (e.g., nausea, vomiting, diarrhea), nervous system (e.g., insomnia, abnormal dreams or nightmares), muscle spasms, bradycardia, and hypotension.

In the clinical trials that were conducted by the sponsor, these types of anticipated events were observed, but at rates that were generally lower than or similar to rates at which these events occur with oral donepezil. The exception is the occurrence of skin reactions that occur due to TDS application. Skin reactions were common in the trials for TDS, but they typically caused a relatively low level of skin irritation. Potential skin sensitization was uncommon. Moreover, these events were rapidly reversible following patch removal. If necessary, use of TDS could be discontinued in individuals who experience intolerable skin reactions, and oral anticholinesterase inhibitors could be started.

There is a serious product quality issue that is reviewed separately by other disciplines. The issue, separation of the patch layers, could potentially result in incorrect dosing in patients in whom the patch separation may occur, or in exposure to donepezil if the patient or caregiver touches the exposed product (b) (4). This is the basis for my recommendation that the product is not approved and that a CR is issued.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting is planned.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The sponsor-proposed label for TDS adheres very closely with the label for Aricept. The

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

proposed label for TDS adds information about TDS dosage, TDS adverse events including application site reactions, instructions on application of TDS, the composition of TDS, and patient counseling information. In general, the proposed labelling for TDS appears adequate and acceptable, with a few exceptions.

A first example regards the proposed indication statement (draft label section 1), which is that:

“(b) (4)”

(b) (4)
The proposed indication statement for Adlarity should be modified to read (modifications highlighted):

“(b) (4)”

A second example regards the most common adverse reactions (draft label section 6.1), in which the cited rates of common adverse reactions are (b) (4)

the rates cited should be those for the higher strength patch (to deliver 10mg/day). (b) (4)

A third minor example is a typo in the patient counseling information (label section 17), in which the phrase “heat pads” should instead be “heating pads.”

10.2. Nonprescription Drug Labeling

This section is not relevant.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are needed because the safety profile of donepezil is well-known since its approval in

1996. The anticipated safety profile of TDS, based purely on the clinical studies that were submitted with this NDA, is anticipated to be similar to or better than that of oral donepezil. Anticipated adverse events (e.g., bradycardia, nausea, vomiting) are easily monitored and detected. Moreover, if needed to manage adverse events, TDS can be discontinued without any withdrawal or rebound effects.

However, overriding the above discussion, there is a serious product quality issue of patch layer separation. This issue is reviewed in critical detail by other disciplines. The relative ease with which the [REDACTED] (b) (4) represents an unacceptable safety risk to the patient, and possibly also to a caregiver who touches the exposed product [REDACTED] (b) (4). This serious product quality issue is the basis for my recommendation that the product is not approved and that a CR is issued.

12. Post-marketing Requirements and Commitments

There will be no PMRs or PMC from a clinical standpoint.

13. Appendices

13.1. References

Alzheimer's Association. 2020 Alzheimer's disease facts and figures. Alzheimer's and Dementia 16(3):391 + [sic].

Aricept Prescribing Information.

Exelon and Exelon patch Prescribing Information.

Hebert LE, Weuve J, et al. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013; 80: 1778-83.

Mayeux R, Sano M, et al. Risk of dementia in first-degree relatives among relatives of patients with Alzheimer's disease and related disorders. Arch Neurol 1991; 48: 269-273.

Razadyne Prescribing Information.

Saunders AM, Strittmatter WJ, et al. Association of apolipoprotein E allele epsilon 4 with

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993; 43: 1467-1472.

13.2. Financial Disclosure

The six IND studies were all covered, and there were no Administrative or Financial Disclosure issues or irregularities in any study. Investigators were not compensated for participating in these studies.

Clinical Review
David A. Hosford, MD PhD
NDA 212,304
Adlarity (donepezil transdermal system) for AD

APPEARS THIS WAY ON ORIGINAL

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/

DAVID HOSFORD
07/07/2020 09:34:34 AM

RANJIT B MANI
07/07/2020 09:44:24 AM