Supplementary Material

Comparison of Steady-State Pharmacokinetics of Donepezil Transdermal Delivery System with Oral Donepezil

Supplementary Table 1. Schedule of Events

		Treatment Phase																					
		Period 1 Day −1 through Day 36										Period 2: Day 37 through Day 72 Period 3 Day 73 through Day 108								Discharge Day 109 Period 3	Early Termination	Follow-Up
Study Procedures	**SCREENING Day −28 to Day −2**	**Day −1**	**Day 1, 8, 15, 22, 29**	**Day 2, 9, 16, 23, 30**	**Day 3, 10, 17, 24, 31**	**Day 4, 11, 18, 25, 32**	**Day 5, 12, 19, 26, 33**	**Day 6, 13, 20, 27, 34**	**Day 7, 14, 21, 28, 35**	**Day 8, 15, 22 & 29**	**Day 36**	**Day 37, 44, 51, 58, 65, 73, 80, 87, 94, 101**	**Day 38, 45, 52, 59, 66, 74, 81, 88, 95, 102**	**Day 39, 46, 53, 60, 67, 75, 82, 89, 96, 103**	**Day 40, 47, 54, 61, 68, 76, 83, 90, 97, 104**	**Day 41, 48, 55, 62, 69, 77, 84, 91, 98, 105**	**Day 42, 49, 56, 63, 70, 78, 85, 92, 99, 106**	**Day 43, 50, 57, 64, 71, 79, 86, 93, 100, 107**	**Day 72 & 108**			
Informed consent	X																					
Inclusion/exclusion criteria	X	X																				
Medical history	X	X																				
Demographics	X																					
Skin type assessment	X																					
Physical examination	X																		X	X	X	
Height and BMI	X																					
Weight	X																		X	X		
12-lead ECG	X	X																	X	X		
Vital signs	X	X	X	---------->															X	X	X	
Hematology, serum chemistry, coagulation, urine analysis	X	X									X								X		X	
COVID-19 test	X	X	---------->																			
Pregnancy test (females only)	X	X									X								X	X	X	
Urine drug and alcohol screen	X	X																				
Serology	X																					
C-SSRS	X	X									X								X		X	
Randomization												X										
Drug administration			X									X										

Study Procedures	SCREENING Day −28 to Day −2	Treatment Phase																				
		Period 1 Day −1 through Day 36										Period 2: Day 37 through Day 72 Period 3 Day 73 through Day 108									Discharge Day 109 Period 3	Early Termination	Follow-Up
		Day −1	Day 1, 8, 15, 22, 29	Day 2, 9, 16, 23, 30	Day 3, 10, 17, 24, 31	Day 4, 11, 18, 25, 32	Day 5, 12, 19, 26, 33	Day 6, 13, 20, 27, 34	Day 7, 14, 21, 28, 35	Day 8, 15, 22 & 29	Day 36	Day 37, 44, 51, 58, 65, 73, 80, 87, 94, 101	Day 38, 45, 52, 59, 66, 74, 81, 88, 95, 102	Day 39, 46, 53, 60, 67, 75, 82, 89, 96, 103	Day 40, 47, 54, 61, 68, 76, 83, 90, 97, 104	Day 41, 48, 55, 62, 69, 77, 84, 91, 98, 105	Day 42, 49, 56, 63, 70, 78, 85, 92, 99, 106	Day 43, 50, 57, 64, 71, 79, 86, 93, 100, 107	Day 72 & 108			
PK sampling				---------->																		
Adhesion assessments			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Skin tolerability assessments			---------->																		X	
Skin photography			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
TDS removal											X	X								X		
Adverse event monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BMI, body mass index; COVID-19, coronavirus disease 2019; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; PK, pharmacokinetic; TDS, transdermal delivery system.

Supplementary Table 2. Dermal response scale

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

Source: US Food and Drug Administration. Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs: Draft Guidance for Industry, 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas

Supplementary Table 3. Scoring of other dermal effects

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

TDS, transdermal delivery system.

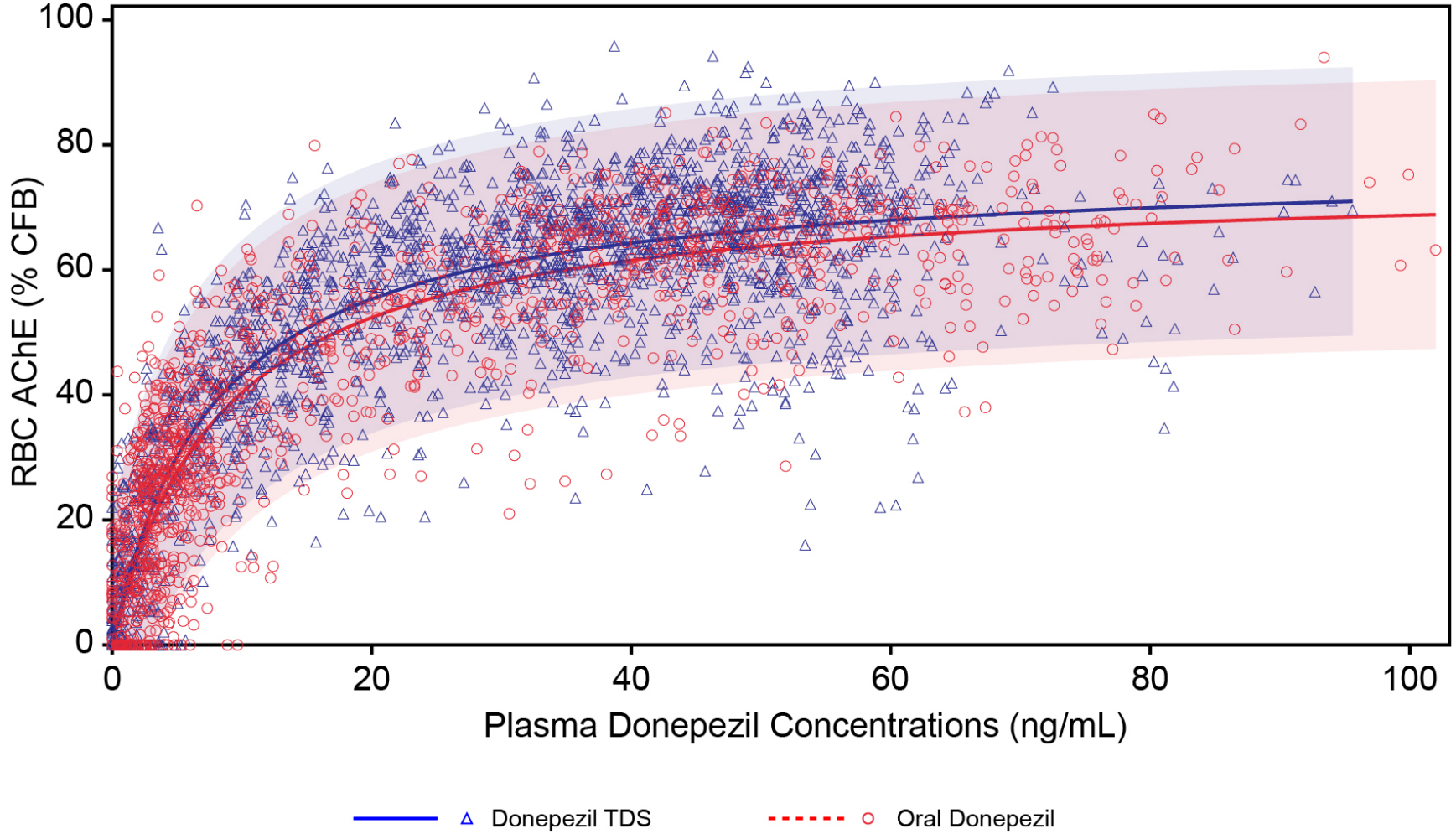
Source: US Food and Drug Administration. Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs: Draft Guidance for Industry, 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas

Supplementary Table 4. Summary of treatment-related AEs and most frequently reported treatment-related AEs in ≥5% of participants overall

MedDRA system organ class MedDRA preferred term	Donepezil TDS 5 mg/d (n=60)	Donepezil TDS 10 mg/d (n=55)	Oral donepezil 10 mg/d (n=56)	Overall (N=60)
	Participants, n (%)			
Related TEAE	25 (41.7)	24 (43.6)	29 (51.8)	44 (73.3)
Gastrointestinal disorders	7 (11.7)	6 (10.9)	29 (51.8)	33 (55.0)
Nausea	3 (5.0)	1 (1.8)	16 (28.6)	18 (30.0)
Constipation	2 (3.3)	3 (5.5)	10 (17.9)	14 (23.3)
Diarrhea	2 (3.3)	1 (1.8)	6 (10.7)	8 (13.3)
Abdominal pain	0	2 (3.6)	1 (1.8)	3 (5.0)
Vomiting	1 (1.7)	0	2 (3.6)	3 (5.0)
General disorders and administration site conditions	16 (26.7)	10 (18.2)	5 (8.9)	26 (43.3)
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	1 (1.7)	1 (1.8)	4 (7.1)	6 (10.0)
Application site irritation	3 (5.0)	0	0	3 (5.0)
Nervous system disorders	8 (13.3)	6 (10.9)	14 (25.0)	21 (35.0)
Headache	5 (8.3)	6 (10.9)	6 (10.7)	14 (23.3)
Dizziness	2 (3.3)	2 (3.6)	8 (14.3)	11 (18.3)
Somnolence	0	0	4 (7.1)	4 (6.7)
Mental impairment	0	1(1.8)	2 (3.6)	3 (5.0)
Psychiatric disorders	9 (15.0)	5 (9.1)	5 (8.9)	15 (25.0)
Nightmare	5 (8.3)	1 (1.8)	1 (1.8)	6 (10.0)
Insomnia	3 (5.0)	3 (5.5)	0	5 (8.3)
Abnormal dreams	1 (1.7)	2 (3.6)	1 (1.8)	4 (6.7)
Musculoskeletal and connective tissue disorders	1 (1.7)	5 (9.1)	4 (7.1)	9 (15.0)
Muscle spasms	1 (1.7)	5 (9.1)	4 (7.1)	9 (15.0)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities, TDS, transdermal system; TEAE, treatment-emergent AE.

Supplementary Figure 1. Individual time-paired values of RBC AChE inhibition (expressed as percentage change from baseline) versus plasma donepezil concentrations for donepezil TDS and oral donepezil at all sampling time points.



The figure depicts the scatter plot of the data, the superimposed fit from the Hill model, and 95% confidence interval bands on the fitted values (donepezil TDS, blue band; oral donepezil, red band). Donepezil 5 mg/d TDS was applied on Day 1 (Week 1), followed by donepezil 10 mg/d TDS applied weekly for 4 consecutive weeks from Week 2 to Week 5. Oral donepezil 5 mg was administered once daily for 7 consecutive days in Week 1, followed by donepezil 10 mg administered once daily for 28 consecutive days from Week 2 to Week 5. CFB, change from baseline; RBC AChE, red blood cell acetylcholinesterase; TDS, transdermal delivery system.