Poster 22

Evaluation of Skin Adhesion and Local Skin Tolerability of Once-Weekly Donepezil Transdermal System: Results of a Phase 1 Trial in Healthy Volunteers

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INTRODUCTION

- Donepezil, a reversible acetylcholinesterase inhibitor, is the most prescribed medication for the treatment of dementia of the Alzheimer's type in patients with mild, moderate, and severe disease.[1]
- The initial dose of donepezil is 5 mg/d for mild to moderate dementia, which can be increased to 10 mg/d after 4 weeks. Both doses are administered orally once a day.[1]
- Dose initiation and escalation of oral donepezil can result in gastrointestinal (GI) side-effects leading to treatment discontinuation, which emphasizes the need for a transdermal delivery system (TDS).[2]
- Donepezil TDS (Adlarity®) is a once-weekly 5- and 10-mg/d donepezil TDS that was recently approved for the treatment of mild, moderate, and severe dementia of the Alzheimer's type.
- In a pivotal phase 1 study in healthy volunteers, the primary end point was steady-state bioequivalence of once-weekly donepezil TDS with once-daily oral donepezil. Secondary end points included TDS skin adhesion and skin tolerability.

OBJECTIVE

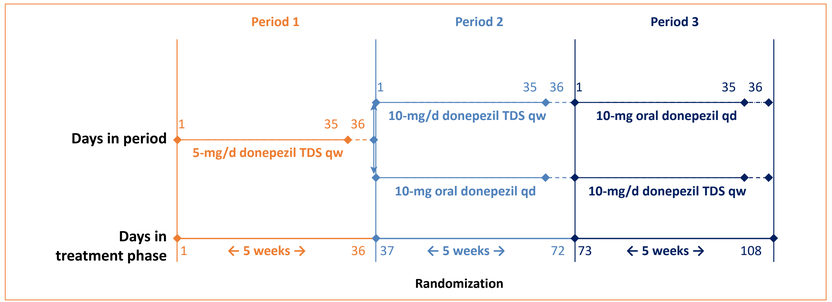
- To evaluate TDS skin adhesion and local skin tolerability, assessed every 12 hours, during the weekly wear-periods of donepezil TDSs.

METHODS

Study Design

- This was an open-label, randomized, 3-period, 3-treatment, crossover phase 1 study (NCT04617782) in healthy volunteers.
- The study consisted of a 28-day screening period followed by 3 treatment periods of 36 days each (**Figure 1**).
- During period 1, all participants received 5-mg/d donepezil TDS applied weekly for 5 consecutive weeks to acclimate participants to the potential cholinergic effects of donepezil.
- During treatment period 2, the participants were randomized to receive either 10-mg/d donepezil TDS applied weekly or 10-mg/d oral donepezil (10-mg Aricept® tablet; Esai, Inc) taken daily; the treatment was switched to the alternate treatment for treatment period 3.

Figure 1. Study design.



qd, once daily; qw, once weekly; TDS, transdermal delivery system.

Assessments

- Adhesion assessments were performed every 12 hours for up to 168 hours after each donepezil TDS application and at the time when a TDS detached completely or was removed. The 168-hour assessment was conducted before TDS removal.
- Skin irritation and tolerability assessments were performed at 0.5, 24, 48, and 72 hours after TDS removal using the dermal response scale recommended by the US Food and Drug Administration (FDA),[3] as shown in **Table 1.**

Table 1. Dermal response scale.[3]

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

TDS, transdermal delivery system.

Statistical Analysis for Adhesion

- Within each treatment, a 1-sided 95% CI was determined for the probability that a randomly selected donepezil TDS maintained ≥75% adhesion throughout the entire wear period.
  - If the 95% lower confidence limit exceeded 80%, it was concluded that ≥80% of donepezil TDSs were ≥75% adhered throughout the 7-day wear period and met the US FDA guidance[4] for acceptable adhesion of TDSs. The 1-sided 95% lower confidence limit was determined using the Jeffreys prior method.

RESULTS

Participant Demographics

- Participant characteristics are shown in **Table 2**.

Table 2. Demographics and baseline characteristics of participants by treatment.

Characteristic	Donepezil TDS		Oral donepezil	Overall
	5 mg/d (n = 60)	10 mg/d (n = 55)	10 mg/d (n = 56)	(N = 60)
Age at informed consent, y				
Mean (SD) [range]	39.8 (9.91) [19-55]	40.5 (9.97) [19-55]	40.5 (9.84) [19-55]	39.8 (9.91) [19-55]
Median (Q1, Q3)	40.0 (32, 49)	42.0 (34, 50)	41.5 (34, 50)	40.0 (32, 49)
Sex, n (%)				
Men	38 (63.3)	33 (60.0)	35 (62.5)	38 (63.3)
Women	22 (36.7)	22 (40.0)	21 (37.5)	22 (36.7)
Race, n (%)				
White	56 (93.3)	52 (94.5)	53 (94.6)	56 (93.3)
Black or African American	3 (5.0)	2 (3.6)	2 (3.6)	3 (5.0)
Asian	1 (1.7)	1 (1.8)	1 (1.8)	1 (1.7)
Height, mean (SD), cm	170.7 (9.5)	170.0 (9.5)	170.3 (9.5)	170.7 (9.5)
Weight, mean (SD), kg	76.5 (10.4)	75.8 (10.2)	75.9 (10.2)	76.5 (10.4)
BMI, mean (SD), kg/m²	26.2 (2.6)	26.2 (2.6)	26.2 (2.6)	26.2 (2.6)

BMI, body mass index; Q1, first quartile; Q3, third quartile; SD, standard deviation; TDS, transdermal delivery system.

Adhesion

- Of 568 TDSs applied (296, 5 mg/d; 272, 10 mg/d), 563 were included in the adhesion analysis.
- The mean percentage (standard deviation) of TDS surface area remaining adhered to the skin during weeks 1-5 was 92.6% (10.9%) for 5-mg/d TDSs and 93.3% (8.8%) for 10-mg/d TDSs.
- The number (%) of TDSs with ≥75% adhesion during weeks 1-5 at all adhesion assessment timepoints during the 1-week wear period was 245 (83.6%) for 5-mg/d TDSs and 232 (85.9%) for 10-mg/d TDSs.
- The number (%) of donepezil TDSs with complete detachment from weeks 1 through 5 during the 7-day wear period was 4 (1.4%) for 5-mg/d donepezil TDSs and 2 (0.7%) for 10-mg/d donepezil TDSs.
- Probability of a TDS maintaining ≥75% adhesion throughout the wear period is shown in **Table 3**.
  - The lower limit of the 1-sided 95% CIs (0.80 for 5-mg/d and 0.82 for 10-mg/d donepezil TDSs) demonstrated that ≥80% of the donepezil TDSs were ≥75% adhered throughout the 7-day wear period.

Table 3. Probability for donepezil TDS maintaining ≥75% adhesion during the entire wear period.

Donepezil TDS	n	Point estimate	Lower limit of the 1-sided 95% CI Jeffreys prior method
5 mg/d	293	0.84	0.80
10 mg/d	270	0.86	0.82

TDS, transdermal delivery system.

Skin Irritation

- For the 5-mg/d donepezil TDSs, 41 of 289 (14.2%) TDSs had a dermal response score of 3 (erythema and papules) at 30 minutes after TDS removal, with subsequent percentage decreases of TDSs with a dermal response score of 3 at 24 hours (10.8%), 48 hours (10.0%), and 72 hours (3.0%) after TDS removal.
  - Two (0.7%) 5-mg/d donepezil TDSs had a dermal response score of 5 (erythema, edema, and papules) at 30 minutes after TDS removal.
- For the 10-mg/d donepezil TDSs, 43 of 268 (16.0%) TDSs had a dermal response score of 3 at 30 minutes after TDS removal, with subsequent percentage decreases of TDSs with a dermal response score of 3 at 24 hours (6.5%), 48 hours (3.4%) and 72 hours (1.4%) after TDS removal.
  - One (0.4%) 10-mg/d donepezil TDS had a dermal response score of 5 at 30 minutes after TDS removal.
- For both 5- and 10-mg/d TDSs, no TDS had a score >3 at 72 hours, and no TDS had scores of 4 (definite edema), 6 (vesicular eruption), and 7 (strong reaction spreading beyond the application site) at any timepoint.
- No participant discontinued early from the study because of skin irritation, and no donepezil TDS was removed because of unacceptable skin irritation.

CONCLUSIONS

- Once-weekly 5- and 10-mg/d donepezil TDSs demonstrated acceptable skin adhesion and skin tolerability, supporting TDS use as treatment for dementia of the Alzheimer's type.

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DISCLOSURES
PNT: consulting fees from AbbVie Inc, AC Immune, Boehringer Ingelheim International GmbH, Chase Pharmaceuticals, Genentech, Inc, Medavante ProPhase Inc, Otsuka Pharmaceutical Company, Ltd, Lilly, AstraZeneca, Avanir Pharmaceuticals, Inc, Merck & Co, Inc, Pfizer Inc, and Roche Pharmaceuticals; research support from AstraZeneca, Avanir Pharmaceuticals, Inc, Lilly, Merck & Co, Inc, Novartis AG, Roche Pharmaceuticals, Functional Neuromodulation Ltd, GE Healthcare, Genentech, Inc, Pfizer Inc, Avid Radiopharmaceuticals, and the Arizona Department of Health Services; stock in Adamas Pharmaceuticals, Inc; and patent for biomarkers of Alzheimer's disease owned by the University of Rochester during the conduct of the study. **RB:** employee of KemPharm, Inc. **CO:** employee of Corium, Inc.

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