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# Bioequivalence and Safety Comparison of Once-Weekly Donepezil Transdermal System With Oral Donepezil: Results of a Phase 1 Pharmacokinetic Study 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 in patients with Alzheimer's disease, which emphasizes the need for a transdermal system (TDS).[2]
- Donepezil TDS (Adlarity®) is a once-weekly 5- and 10-mg/d donepezil TDS, which was recently approved for the treatment of mild, moderate, and severe dementia of the Alzheimer's type.

## OBJECTIVE

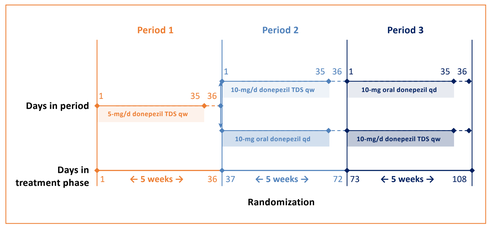
- To compare the steady-state pharmacokinetics (PK) and safety and tolerability of once-weekly 5- and 10-mg/d donepezil TDS application with once-daily oral 10-mg donepezil (oral donepezil) administration in healthy volunteers.

## 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. The 5 weeks of 5-mg/d treatment also allowed donepezil to reach steady-state levels for the measurement of steady-state PK.
- 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

- For PK assessments of all participants, blood samples were obtained predose and at specified timepoints postdose.
  - PK parameters evaluated included:
    - Maximum (max) observed plasma concentration at steady state (ss) ($C_{max,ss}$; week 5)
    - Minimum (min) observed nonzero plasma concentration over a dosage interval at steady state ($C_{min,ss}$; week 5)
    - Area under the plasma concentration versus time curve during a 1-week period at steady state ($AUC_{0\text{-}168,ss}$)
    - Time to reach $C_{max,ss}$ ($T_{max}$)
    - Percent peak-to-trough fluctuation ($FLUCP_{ss}$) at steady state in week 5
- AEs were continuously monitored from the administration of the first dose of study drug until either the follow-up visit or early termination from the study.

### Statistical Analysis

- For the comparison of 5-mg/d and 10-mg/d donepezil TDS versus oral donepezil, the analysis was performed using an analysis of variance model.
- The PK parameter values for 5-mg/d donepezil TDS were dose normalized (by multiplying with 2) before the analysis.
- The relative bioavailability at steady state of the 5- and 10-mg/d donepezil TDS (tests) relative to oral donepezil (reference), plasma donepezil exposure characterized by $C_{max,ss}$ and $AUC_{0\text{-}168,ss}$, was assessed and compared using bioequivalence criteria. Bioavailability for donepezil was concluded if the 90% CIs of the least-squares geometric means for the log-transformed $AUC_{0\text{-}168,ss}$ and $C_{max,ss}$ ratios fell within the acceptable range of 0.80 to 1.25.

## RESULTS

### Participant Demographics

- Participant characteristics are shown in **Table 1**.

**Table 1. Demographics and baseline characteristics of participants by treatment.**

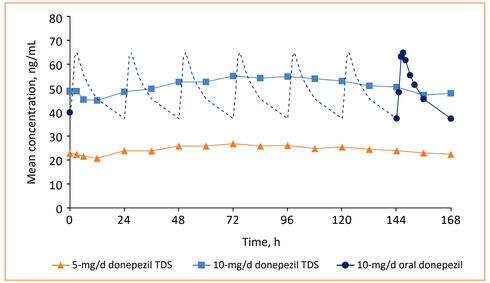
| | Donepezil TDS 5 mg/d (n = 60) | Donepezil TDS 10 mg/d (n = 55) | Oral donepezil 10 mg/d (n = 56) | Overall (N = 60) |
|---|---|---|---|---|
| Age at informed consent, y | | | | |
| Mean (SD) [range] | 39.8 (9.91) [19-55] | 40.5 (9.97) [19-55] | 40.5 (9.84) [19-55] | 39.8 (9.91) [19-55] |
| Median (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.*

### Pharmacokinetics and Relative Bioavailability

- The mean steady-state plasma concentration-time PK profiles of donepezil TDS and oral donepezil are shown in **Figure 2**.

**Figure 2. Mean steady-state (week 5) plasma concentration-time curves for 5-mg/d donepezil TDS, 10-mg/d donepezil TDS, and 10-mg/d oral donepezil.**




*Donepezil TDS was applied weekly for 5 weeks; oral donepezil was administered daily for 5 weeks. The replicated steady-state pharmacokinetic profile for oral donepezil on days 1-6 is shown as a dashed line to represent that they are replicated from day 7 (144-168 hours).*
*TDS, transdermal delivery system.*

- Steady-state (week 5) mean values for $C_{max,ss}$, $C_{min,ss}$, and $AUC_{0\text{-}168,ss}$ were similar for 5-mg/d donepezil TDS (dose-normalized to the 10-mg/d dose before analysis by multiplying concentrations by 2), 10-mg/d donepezil TDS, and oral donepezil (**Table 2**).
  - Median $T_{max}$ was considerably higher for 5-mg/d donepezil TDS (72 hours) and 10-mg/d donepezil TDS (84 hours) than for oral donepezil (2 hours).
  - $FLUCP_{ss}$ was higher for oral donepezil than for 5- and 10-mg/d donepezil TDS treatments.
  - Based on results from the steady-state assessment, steady state for donepezil was reached by day 22 for 5- and 10-mg/d donepezil TDSs and by day 8 for oral donepezil.

**Table 2. Plasma donepezil PK parameters at week 5.**

| Parameter | Donepezil TDS 5 mg/d[a] (n = 56) | Donepezil TDS 10 mg/d (n = 53) | Oral donepezil 10 mg/d (n = 53) |
|---|---|---|---|
| $C_{max,ss}$, mean (SD), ng/mL | 59.8 (18.2) | 62.5 (20.0) | 70.6 (19.4) |
| $C_{min,ss}$, mean (SD), ng/mL | 41.0 (14.2) | 43.2 (15.6) | 39.9 (14.6) |
| $AUC_{0\text{-}168,ss}$, h · ng/mL | 8732.1 (2760.3) | 9099.0 (2972.1) | 8462.6 (2558.0) |
| $T_{max,ss}$, median (range), h | 72.0 (0-156.0) | 84.0 (0-120.0) | 2.0 (0-4.1) |
| $FLUCP_{ss}$, mean (SD), % | 36.7 (14.8) | 35.8 (14.5) | 64.9 (23.7) |

*$AUC_{0\text{-}168,ss}$, area under the plasma concentration versus time curve during a 1-week period at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum observed nonzero plasma concentration at steady state; $FLUCP_{ss}$, percent peak-to-trough fluctuation at steady-state; SD, standard deviation; TDS, transdermal delivery system; $T_{max,ss}$, time to reach $C_{max,ss}$.*
*[a]Concentrations for 5-mg/d donepezil TDS were dose-normalized to the 10-mg/d dose before analysis by multiplying concentrations for 5-mg/d dose by 2.*

- For 10-mg/d donepezil TDS versus oral donepezil, the 90% CIs for the geometric mean ratios of $C_{max,ss}$ and $AUC_{0\text{-}168,ss}$ were within the accepted 0.80 to 1.25 range for establishing bioequivalence (**Table 3**).
- For 5-mg/d donepezil TDS (dose normalized) versus oral donepezil, the 90% CIs for the geometric mean ratio of $C_{max,SS}$ and $AUC_{0\text{-}168,ss}$ were within the range for bioequivalence (**Table 3**).

**Table 3. Relative bioavailability of 10-mg/d and 5-mg/d donepezil TDS vs oral donepezil.**

| Dependent variable | Donepezil TDS geometric mean[a] | Oral donepezil geometric mean[a] | Adjusted GMR, %[b] | *P* value[c] | 90% CI |
|---|---|---|---|---|---|
| **10-mg/d donepezil TDS vs 10-mg/d oral donepezil (n = 52)** | | | | | |
| $C_{max,ss}$, ng/mL | 59.6 | 67.2 | 88.7 | .02 | (0.82-0.96) |
| $AUC_{0\text{-}168,ss}$, h · ng/mL | 8678.7 | 7992.3 | 108.6 | .08 | (1.01-1.17) |
| **5-mg/d donepezil TDS vs 10-mg/d oral donepezil (n = 51)** | | | | | |
| $C_{max,ss}$, ng/mL | 57.8 | 67.1 | 86.1 | .002 | (0.80-0.93) |
| $AUC_{0\text{-}168,ss}$, h · ng/mL | 8401.9 | 7979.1 | 105.3 | .26 | (1.00-1.14) |

*$AUC_{0\text{-}168,ss}$, area under the plasma concentration versus time curve during a 1-week period at steady state; $C_{max,ss}$, maximum concentration at steady state; GMR, geometric mean ratio; TDS, transdermal delivery system.*
*[a]Geometric mean obtained by exponentiating the least-squares mean.*
*[b]Adjusted GMR (%) = 100 × [geometric mean (donepezil TDS)/geometric mean (oral donepezil)]. The GMR and its 90% CI were obtained by exponentiation of the difference between the treatment least-squares means on the logarithmic scale and by exponentiation of the limits of the 90% CI for the difference, respectively.*
*[c]P value from the mixed model.*

### Safety

- AEs were reported in 80.0% of participants (53.3% for the 5-mg/d donepezil TDS, 54.5% for the 10-mg/d donepezil TDS, and 57.1% for oral donepezil; **Table 4**).
  - For most participants (44/60 [73.3%]), AEs were reported as mild in severity; 4 participants (6.7%; 2 on 5-mg/d donepezil TDS, 1 on 10-mg/d donepezil TDS, and 1 on oral donepezil) had AEs of moderate severity; and none had AEs of severe severity. No serious AEs or deaths were reported. No AEs led to discontinuation of study treatment or early termination.
  - GI disorders were more frequent with oral donepezil than with donepezil TDS (**Table 4**).
  - More participants reported dizziness, fatigue, and somnolence with oral donepezil than with donepezil TDS. Application-site pruritis, application-site dermatitis, abdominal pain, and insomnia were more frequent with 10-mg/d donepezil TDS than with oral donepezil (**Table 4**).
  - There were no clinically important changes in clinical laboratory values, vital signs, electrocardiograms, or physical examinations across all treatments. No occurrences of suicidal thoughts or ideation were reported.

**Table 4. Overall summary of treatment-emergent AEs and most frequently reported AEs in ≥5% of participants overall.**

| | 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 (%) | | | |
| **TEAEs** | 32 (53.3) | 30 (54.5) | 32 (57.1) | 48 (80.0) |
| **Related TEAEs** | 25 (41.7) | 24 (43.6) | 29 (51.8) | 44 (73.3) |
| **AEs by MedDRA system organ class** **MedDRA preferred terms** | | | | |
| **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) |
| Diarrhea | 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) |

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

## CONCLUSIONS

- Both the 10-mg/d and dose-normalized 5-mg/d donepezil TDS strengths were bioequivalent to oral donepezil on a milligram-per-day basis.
- Use of donepezil TDS was associated with fewer treatment-emergent GI disorders and central nervous system–associated adverse effects than oral donepezil, which may lead to better tolerability and compliance among patients.

**REFERENCES**

1. Kumar A, et al. Donepezil. In: StatPearls. StatPearls Publishing; 2021.
2. Farlow MR, et al. *Clin Ther*. 2010;32(7):1234-1251.

**DISCLOSURES**

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