INTRODUCTION

• Oral donepezil, a reversible acetylcholinesterase inhibitor, is the most used treatment for dementia of the Alzheimer type.
• Once-weekly donepezil transdermal delivery system (TDS; ADELITY™) was approved in 2022 by the US Food and Drug Administration for the treatment of mild, moderate, and severe dementia of the Alzheimer type.
• A previous study showed that 10 mg/d of dose-normalized 5 mg/d donepezil TDSs are bioequivalent to 10 mg/d of oral donepezil, with an acceptable skin adhesion and safety profile.1

OBJECTIVE

• The objective was to assess the skin irritation and sensitization potential of once-weekly 5 mg/d donepezil TDS.

METHODS

Study Design

• This was a placebo (vehicle) TDS-controlled, randomized, double-blind phase 1 trial (NCT03397862).
• Healthy adult volunteers aged ≥40 years with Fitzpatrick skin type I, II, or III and without a history of severe allergies to medical adhesive tapes and dressings were evaluated for the primary end points of skin irritation and sensitization potential. Secondary end point of skin adhesion was assessed.
• The study design is shown in Figure 1.

Figure 1. Study design.

Results

Analysis Populations

• Safety population was defined as all randomized participants who had ≥1 study TDS applied.
• Per-protocol (PP) skin irritation population was defined separately for each treatment (ie, donepezil TDS and placebo TDS). The PP skin irritation population for each treatment included all TDSs applied sequentially to the same site for the entire 21-day induction phase (without any period of detachment longer than 24 hours). This differs from the donepezil TDS prescribing information, which indicates that the TDS application site should be rotated to minimize skin irritation and the same body site should not be used within 14 days.

Assessments

• The combined skin irritation score (CSIS) was based on the sum of the Dermal Response Scale score and Other Effects Scale score (Table 1).

Skin irritation scoring was performed 30 minutes after TDS removal on days 8, 15, and 22 in the induction phase.

Table 1. Dermal Response Scale and Other Effects Scale scores.

<table>
<thead>
<tr>
<th>Dermal Response Scale</th>
<th>Other Effects Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin appearance</td>
<td>Score</td>
</tr>
<tr>
<td>No evidence of irritation</td>
<td>0</td>
</tr>
<tr>
<td>Minimal erythema, barely perceptible</td>
<td>1</td>
</tr>
<tr>
<td>Glazing with peeling and cracking</td>
<td>2</td>
</tr>
</tbody>
</table>
| Erythema and papules | 3
| Glazing with frissures/dried superficial exudate film covering all or part of the patch site/small petechial erosions and/or scales | 3
| Definite edema | 4
| Vascular eruption | 5
| Strong reaction spreading beyond the application site | 7

| Adhesion of the TDSs was assessed within 2 hours after TDS application and before TDS removal or if the patient reported lifting or detachment of the patch. Adhesion assessment scale scoring ranged from 0 (100% adhesion) to 11 (detached).

| Adverse events (AEs) were continuously monitored until the completion of the study.

Statistical Analyses

• The primary analysis was descriptive of the mean CSIS during the induction period and the proportion of participants potentially sensitized to each treatment.

RESULTS

Participants

• Among the 256 participants who were randomized and received ≥1 dose of any treatment, the mean (SD) age was 54.3 ± 9.4 years, 48% were aged 50-64 years, 16% were aged 65 years, and 9.4% were women (Table 2).

• The participants’ demographics and baseline characteristics are shown in Table 2.

Skin irritation and Sensitization

• After the first weekly TDS application (day 8) in the induction phase, the incidence of CSIS of 0 and 1 was similar between donepezil TDSs and placebo TDSs (Figure 2).

• The average (SD) of the mean CSIS (ie, the sum of the combined Dermal Response and Other Effects Scale scores obtained on days 8, 15, and 22) divided by 3 was 0.55 (0.78) of a possible maximum of 7, indicating none to minimal skin irritation for donepezil TDS and, 0.19 (0.33), indicating no skin irritation for placebo TDS (treatment difference, 0.36; 95% CI, 0.43 to 0.25).

• TDS CSISs during the induction phase appeared to be independent of age, ethnicity, or sex, although there was a slight numerical trend of better skin tolerability in the ≥65-year-old versus <65-year-old age group (Figure 3).

• Of the PP skin irritation population receiving donepezil TDS, 4 of 30 aged ≥65 years (13.3%) had a CSIS ≥2. By comparison, 28 of 91 participants aged 50-64 years (30.8%) and 18 of 74 participants aged <50 years (24.4%) had CSISs ≥2.

• The incidence of maximum CSISs >1 for men was 29.9% with donepezil TDS and 12.0% with placebo TDS; for women, it was 23.9% with donepezil TDS and 2.5% with placebo TDS.

• Of 98 participants, 4 (2.0%) were considered potentially sensitized to donepezil TDS treatment, and no participants were potentially sensitized to placebo TDS.

Table 2. Participant’s demographics and baseline characteristics (safety population).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Participants (N = 256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>54.3 (9.4)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td>&lt;50 y 92 (35.9) 50 to &lt;65 y 123 (48.0) ≥65 y 41 (16.0)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Men 104 (40.6) Women 152 (59.4)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>Hispanic or Latino 72 (28.1) Not Hispanic or Latino 184 (71.9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White 254 (99.2) Multiracial 1 (0.4) American Indian/Alaska Native 1 (0.4)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>78.8 (14.4)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>28.0 (3.7)</td>
</tr>
<tr>
<td>Skin type, n (%)</td>
<td>I 0 II 7 (2.7) III 86 (33.6) IV 63 (24.7)</td>
</tr>
</tbody>
</table>

Table 3. Dermal response scale scores during the induction phase (PP skin irritation population).

<table>
<thead>
<tr>
<th>Day 22</th>
<th>Donepezil TDS CSIS</th>
<th>Placebo TDS CSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DISCUSSION

• Once-weekly 5 mg/d donepezil TDS demonstrated minimal skin irritation under use conditions of 3 consecutive weekly patch applications to the same skin site and minimal sensitization potential:

• Participants aged ≥65 years had better skin irritation scores, indicating better skin tolerability relative to other age groups.

• Placing consecutive TDSs to the same site could worsen skin tolerability score versus rotating the TDSs to different sites as instructed in the donepezil TDS prescribing information.

CONCLUSION

• Once-weekly 5 mg/d donepezil TDS was well tolerated when applied to any skin site and had essentially no lift (treatment difference, −0.34; 95% CI, 0.43 to 0.25) when compared to placebo TDS (treatment difference, −0.34; 95% CI, 0.43 to 0.25).

• The incidence of CSISs >1 for men was 29.9% with donepezil TDS and 12.0% with placebo TDS; for women, it was 23.9% with donepezil TDS and 2.5% with placebo TDS.

ACKNOWLEDGMENTS

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• They also thank the study investigators, study site personnel, and the employees of Corium, Inc., who supported this study.

REFERENCES

1. Data on file, Corium Inc., San Francisco, CA, USA.
2. This study was funded by Corium Inc., San Francisco, CA, USA.
3. The authors thank all study participants for their voluntary participation.
4. They also thank the study investigators, study site personnel, and the employees of Corium, Inc., who supported this study.

The primary analysis was descriptive of the mean CSIS during the induction period and the proportion of participants potentially sensitized to each treatment.