Poster LP34

A Randomized Double-Blind Study to Assess the Skin Irritation and Sensitization Potential of Once-Weekly Donepezil Transdermal Delivery System

Marwan Sabbagh, MD[1]; Philip Mathew, MD[2]; and Alan Blau, PhD[3]

[1]Barrow Neurological Institute, Phoenix, AZ, USA; [2]Novum Pharmaceutical Research Services, Toronto, Ontario, Canada; formerly with Celerion, Lincoln, NE, USA, where the work was conducted; and [3]Corium Inc, Grand Rapids, MI, USA

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; ADLARITY®) 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 and 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.

Screening phase	• 30 d before TDS application
Induction phase	• 21 d of weekly 5-mg/d donepezil TDS and a placebo TDS to opposite sides of their backs – 5-mg/d donepezil TDS applied to the right side of the back and placebo TDS to the left side or vice-versa
Rest phase	• After completion of the induction phase, participants entered a 14-d rest period followed by a challenge phase for skin sensitization assessments
Challenge phase	• Donepezil TDS and placebo TDS were applied to naive skin sites on opposite sides of the back in a randomized manner • Treatment duration of 48 h followed by a 3-d observation period
Rest and rechallenge phase	• 4–8-wk rest phase • Some participants underwent a 48-h rechallenge phase if the participant was designated as potentially sensitized to 1 or both TDSs

TDS, transdermal delivery system.

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.[2]

Dermal Response Scale		Other Effects Scale	
Skin appearance	**Score**	**Skin appearance**	**Score**
No evidence of irritation	0	None observed/slightly glazed appearance	0
Minimal erythema, barely perceptible	1	Marked glazed appearance	1
Definite erythema, readily visible; minimal edema; or minimal papular response	2	Glazing with peeling and cracking	2
Erythema and papules	3	Glazing with fissures/dried serous exudate film covering all or part of the patch site/small petechial erosions and/or scabs	3
Definite edema	4		
Erythema, edema, and papules	5		
Vesicular eruption	6		
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).[3,4]
- 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 years (9.4 years); 48% were aged 50-64 years, 16% were aged ≥65 years, and 59.4% were women (**Table 2**).
- The participants' demographics and baseline characteristics are shown in **Table 2**.

Skin Irritation and Sensitization

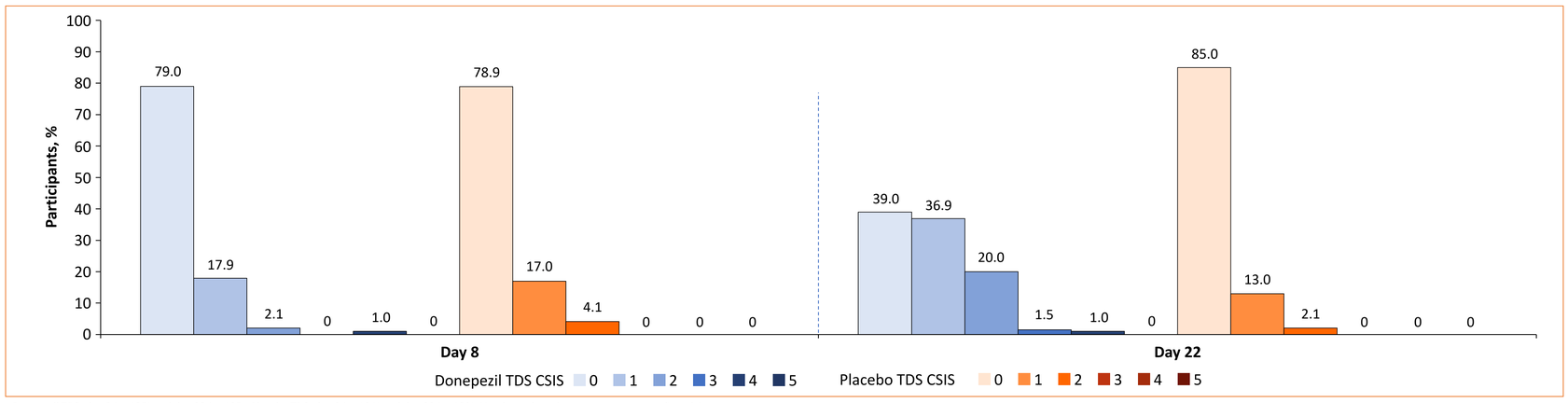
- After the first weekly TDS application (day 8) in the induction phase, the incidence of CSISs of 0 and 1 was similar between donepezil TDSs and placebo TDSs (**Figure 2**).
  - Two donepezil TDSs (1.0%) had a score of 4, and there were none with scores ≥5.
  - There were no scores >2 for the placebo TDSs.
- At the third weekly TDS application (day 22) in the induction phase, CSISs were higher for donepezil TDS versus the placebo TDS (**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 (0.35), indicating no skin irritation for placebo TDS (treatment difference, −0.34 [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 22% with donepezil TDS and 2.5% with placebo TDS.
- Of 198 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).

Parameter	Participants (N = 256)
Age, mean (SD), y	54.3 (9.4)
Age group, n (%)	
<50 y	92 (35.9)
50 to <65 y	123 (48.0)
≥65 y	41 (16.0)
Sex, n (%)	
Men	104 (40.6)
Women	152 (59.4)
Ethnicity, n (%)	
Hispanic or Latino	72 (28.1)
Not Hispanic or Latino	184 (71.9)
Race, n (%)	
White	254 (99.2)
Multiracial	1 (0.4)
American Indian/Alaska Native	1 (0.4)
Weight, mean (SD), kg	78.8 (14.4)
Body mass index, mean (SD), kg/m²	28.0 (3.7)
Skin type, n (%)	
I[a]	7 (2.7)
II[b]	86 (33.6)
III[c]	163 (63.7)

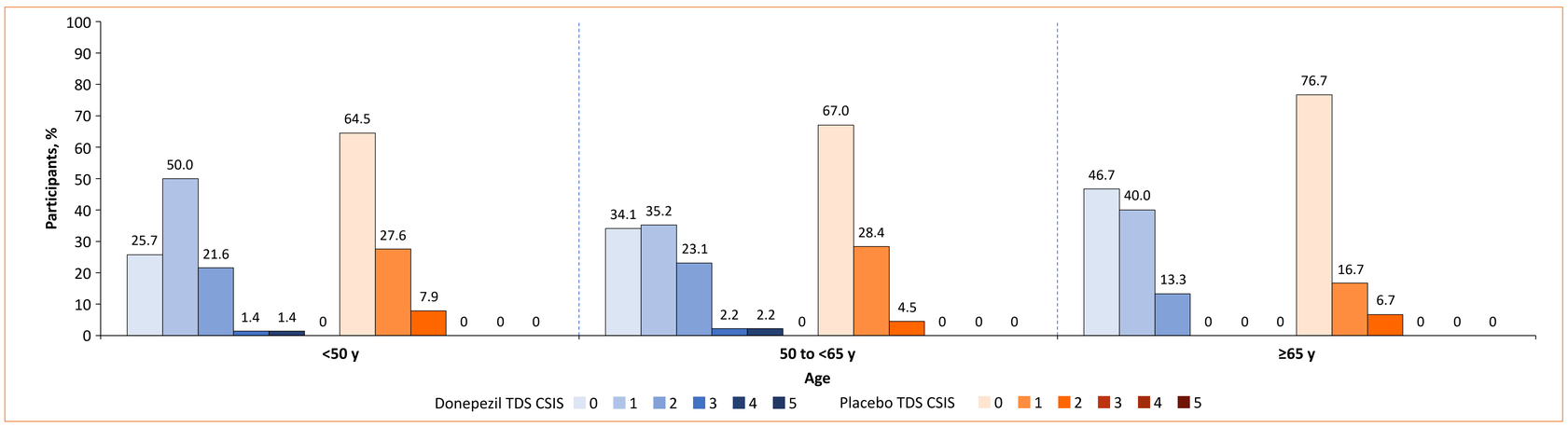
[a]*Always burns; never tans.*
[b]*Usually burns; tans with difficulty.*
[c]*May burn initially but tans easily.*

Figure 2. CSISs during the induction phase for donepezil TDS and placebo TDS (PP skin irritation population).



Donepezil TDS: day 8 (n=195) and day 22 (n=195). Placebo TDS: day 8 (n=194) and day 22 (n=193). Numbers above bars are percentages of participants.
CSIS, combined skin irritation score; PP, per protocol; TDS, transdermal delivery system.

Figure 3. Frequency distribution of TDS CSISs by age (PP skin irritation population).



Donepezil TDS: age <50 y (n=74), 50 to <65 y (n=91), and ≥65 y (n=30). Placebo TDS: age <50 y (n=76), 50 to <65 y (n=88), and ≥65 y (n=30). Numbers above bars are percentages of participants.
CSIS, combined skin irritation score; PP, per protocol; TDS, transdermal delivery system.

Skin Adhesion

- In general, on a weekly basis, good adhesion was observed (ie, ≥90%) for TDS of either treatment (except donepezil TDS on day 22, which was 88.4%) and had essentially no lift from skin (score of 0 [100% adhesion] to 1 [90% to <100% adhesion]).
  - In total, 12 patches (7 [1.0%] donepezil TDS; 5 [0.7%] placebo TDS) detached during the study.

Adverse Events

- Of the 256 participants, 195 (76.2%) reported at least 1 treatment-emergent adverse event (TEAE) during the study.
  - Of these, 186 participants (72.7%) had ≥1 drug-related TEAE, and 10 participants (3.9%) had ≥1 TEAE leading to study drug discontinuation.
  - TEAEs included application site pruritus (40.2%), headache (18.4%), nausea (18.0%), abnormal dreams (18.0%), muscle spasms (16.8%), and insomnia (10.2%).
  - No serious AEs were reported during the study.

CONCLUSION

- 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.

REFERENCES

1. Tariot PN, et al. *J Alzheimers Dis.* 2022;9:1-12.
2. 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
3. Food and Drug Administration. Assessing adhesion with transdermal delivery systems and topical patches for abbreviated new drug applications: draft guidance for industry, 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry
4. European Medicines Agency. Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11WC500177884.pdf.

DISCLOSURES

MS: ownership interest (stock or stock options) in NeuroTau uMethod Health, Versanum, Athira, TransDermix, Seq BioMarque, NeuroReserve, Cortexyme/Quince Therapeutics, Lighthouse Pharmaceuticals, and Alzheon; consulting for Roche-Genentech, Eisai, Lilly, Synaptogenix, NeuroTherapia, T3D, Signant Health, and Novo Nordisk; and board of directors for EIP Pharma. **PM:** nothing to disclose. **AB:** employee of Corium, Inc.

This study was funded by Corium, Inc, Grand Rapids, MI, USA.

Medical writing support for the development of this poster, under the direction of the authors, was provided by Charlette Tiloke, PhD, and Gautam Bijur, PhD, with editing support from Mary C. Wiggin, all of Ashfield MedComms, an Inizio company, and funded by Corium, Inc (Grand Rapids, MI, USA).