JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(4):428-436 / https://doi.org/10.3988/jcn.2022.18.4.428

A Multinational, Multicenter, Randomized, Double-Blind, Active Comparator, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Donepezil Transdermal Patch in Patients With Alzheimer's Disease

Hyun Jeong Han[a]
Mee Young Park[b]
Kyung Won Park[c]
Kee Hyung Park[d]
Seong Hye Choi[e]
Hee-Jin Kim[f], Dong Won Yang[g]
Esther Gunaseli A/P M. Ebenezer[h]
Yuan-Han Yang[i]
Gurudev M. Kewalram[j]
Seol-Heui Han[k] and
on Behalf the IPI-301 Study

[a]Department of Neurology, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea
[b]Department of Neurology, Yeungnam University Medical Center, Daegu, Korea
[c]Department of Neurology, Dong-A Medical Center, Dong-A University College of Medicine, Busan, Korea
[d]Department of Neurology, College of Medicine, Gachon University Gil Medical Center, Incheon, Korea
[e]Department of Neurology, Inha University School of Medicine, Incheon, Korea
[f]Department of Neurology, Hanyang University College of Medicine, Seoul, Korea
[g]Department of Neurology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea
[h]Hospital Raja Permaisuri Bainun, Palac, Malaysia
[i]Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan
[j]Prince Charles Hospital, Brisbane, Australia
[k]Department of Neurology, Konkuk University School of Medicine and Konkuk University Medical Center, Seoul, Korea

Received March 8, 2022
Revised May 18, 2022
Accepted May 18, 2022

Correspondence
Seol-Heui Han, MD, PhD
Department of Neurology, Konkuk University School of Medicine and Konkuk University Medical Center, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea
Tel +82-2-2030-7561
Fax +82-2-2030-7018
E-mail alzdoc@kuh.ac.kr

Background and Purpose Oral administration of cholinesterase inhibitors is often associated with adverse gastrointestinal effects, and so developing an alternative administration route, such as transdermal, is urgently needed. The primary objective of this study was to determine the efficacy and safety of the IPI-301 donepezil transdermal patch compared with donepezil tablets (control) in mild-to-moderate probable Alzheimer's disease (AD).

Methods This prospective, randomized, double-blind, double-dummy, two-arm parallel, multicenter trial included 399 patients, among whom 303 completed the trial. For randomization, the patients were stratified based on previous treatment and donepezil dose; patients in each stratum were randomized to the test and control groups at a 1:1 ratio.

Results The difference between the control group and the IPI-301 group, quantified as the Hodges–Lehmann estimate of location shift, was 0.00 (95% confidence interval: -1.00 to 1.33), with an upper limit of less than 2.02. The change in Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) score differed significantly between the IPI-301 and control groups (p=0.02). However, the changes in the full-itemized ADCS-ADL scores at week 24 did not differ significantly between the two groups. There were no differences between the two groups regarding the scores for the Clinician Interview-Based Impression of Change (p=0.9097), Mini-Mental State Examination (p=0.7018), Neuropsychiatric Inventory (p=0.7656), or Clinical Dementia Rating (p=0.9990). Adverse events, vital signs, and laboratory test results were comparable between the two groups.

Conclusions IPI-301 was safe and efficacious in improving cognitive function in patients with mild-to-moderate AD.

Keywords donepezil transdermal patch; Alzheimer's disease; efficacy; safety; acetylcholinesterase inhibitor

INTRODUCTION

Alzheimer's disease (AD) is the most common type of senile dementia, affecting 6–8% of people aged >65 years and nearly 30% of people aged >85 years.[1] Every 5 years there is a twofold increase in the number of people aged >60 years affected by AD, and so AD is expected to affect more than 115 million people worldwide by 2050.[2] Donepezil, an oral cholinesterase inhibitor, is widely used in clinical practice to treat mild-to-severe AD symptoms. The oral cholinesterase inhibitor class of drugs is effective for improving the cognitive and global functioning of patients with AD, and is the main pharmacological intervention used in the clinical management of AD.[3,4] However, the incidence of adverse events (AEs) asso-

ciated with donepezil (e.g., abdominal pain, nausea and vomiting, anorexia, and diarrhea) increases with the administered dose, which can lead to difficulty in achieving and maintaining high therapeutic doses in clinical practice.[5-7] These dose-dependent adverse symptoms linked to cholinergic hyperstimulation are related to plasma concentration fluctuations.[8] A novel therapeutic approach using a transdermal delivery system may be a solution to the above-mentioned limitations. Delivering a drug through the skin directly into the bloodstream avoids first-pass effects, therefore reducing rates of nausea and vomiting.[9,10] Compared with oral formulations, transdermal patch formulations can reduce the maximum systemic drug concentration by decreasing the absorption rate, which decreases the necessary dosing frequency; this lower frequency leads to improved treatment compliance. Indeed, this administration route is particularly useful in patients with chronic neurological disorders because it can circumvent their unwillingness or inability to swallow; it also avoids the need for intramuscular injections or intravenous infusions.[11,12] Moreover, it provides stable blood drug levels over an extended period and improves patient compliance because there is no requirement to manage medication timing or carry pills.[13] The present study was performed to determine the efficacy and safety of IPI-301 donepezil transdermal patches in comparison with oral donepezil tablets after 24 weeks of treatment in patients with mild-to-moderate AD.

METHODS

Study design

This clinical trial had a phase III prospective, double-dummy, double-blind, multidose, active comparator, randomized, two-arm parallel, cohort expansion, multicenter design; it began on October 11, 2017 and ended on July 20, 2020. The trial was performed at 46 study sites: 22 in Republic of Korea, 12 in Taiwan, 4 in Malaysia, and 8 in Australia. For randomization, the patients were stratified based on their previous experiences with and doses of donepezil; each stratum was randomized to either the IPI-301 or oral donepezil (control) group at a 1:1 ratio. The test drug, a transdermal patch, or its placebo applied twice a week (3- or 4-day intervals) before bedtime. If it was not possible to apply the patch before bedtime, it was applied at a different time point based on the judgment of the investigator. Follow-ups were performed whenever the patch was applied. The control drug or its placebo was administered orally once daily before bedtime. If it was not possible to take the drug before bedtime, it was administered at the appropriate time based on the judgment of the investigator and a follow-up was carried out after the tablet was administered. All patients completed the following questionnaires: Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog),[14] Clinician Interview-Based Impression of Change plus caregiver input (CIBIC-Plus),[15] Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL),[16] Neuropsychiatric Inventory (NPI),[17] and the Columbia Suicide Severity Rating Scale (C-SSRS).[18] The patients were administered either IPI-301 or oral donepezil (or rescue medication if necessary) for 24 weeks as specified in the study design with regard to doses and dosage regimens. Data regarding treatment dosing (oral tablet intake and patch application) and patch removal time points were also collected from the provided patient diaries over 24 weeks. Visits were carried out at 6-week intervals throughout the treatment period. Donepezil-naïve patients were administered the assigned treatment at a lower dose (i.e., 87.5 mg/25 cm^2 IPI-301 or 5-mg donepezil tablets) for the first 6 weeks and then changed to the higher dose (i.e., 175 mg/50 cm^2 IPI-301 or 10-mg donepezil tablets) at the third visit if no serious adverse drug reactions or other clinically significant symptoms occurred. To monitor the safety of drug-naïve patients, follow-up phone calls were performed at weeks 2 and 4 after the dose increase at the third visit. AE occurrences and concomitant medication use were also evaluated. The treatment visits ended at week 24 after the first treatment, and safety was monitored until 4 weeks after the final dose (Fig. 1).

Participants

The study population consisted of patients with mild-to-moderate AD, all of whom had a clinical diagnosis of probable AD according to the criteria of the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders,[19] National Institute of Neurological and Communicative Disorders and Strokes, and Alzheimer's Disease and Related Disorders Association.[20] Our inclusion criteria were as follows: age 50−85 years prior treatment with donepezil at 5 or 10 mg/day for at least 3 months prior to screening or no prior treatment with donepezil (naïve patients), mild-to-moderate AD defined as Mini-Mental State Examination (MMSE) score[21] ≥10 and ≤26 at screening, global Clinical Dementia Rating (CDR) score[22] ≤2, presence of a reliable caregiver sufficiently familiar with the patient who could provide accurate information to the investigators, and both the patient and their caregiver agreeing to participate. The exclusion criteria were as follows: any diagnosis of possible, probable, or confirmed vascular dementia according to the criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences;[23] history or evidence (e.g, computed tomography (CT) or magnetic resonance imaging (MRI) findings obtained within the last 12 months or at screening) of other central nervous system disorders (cere-

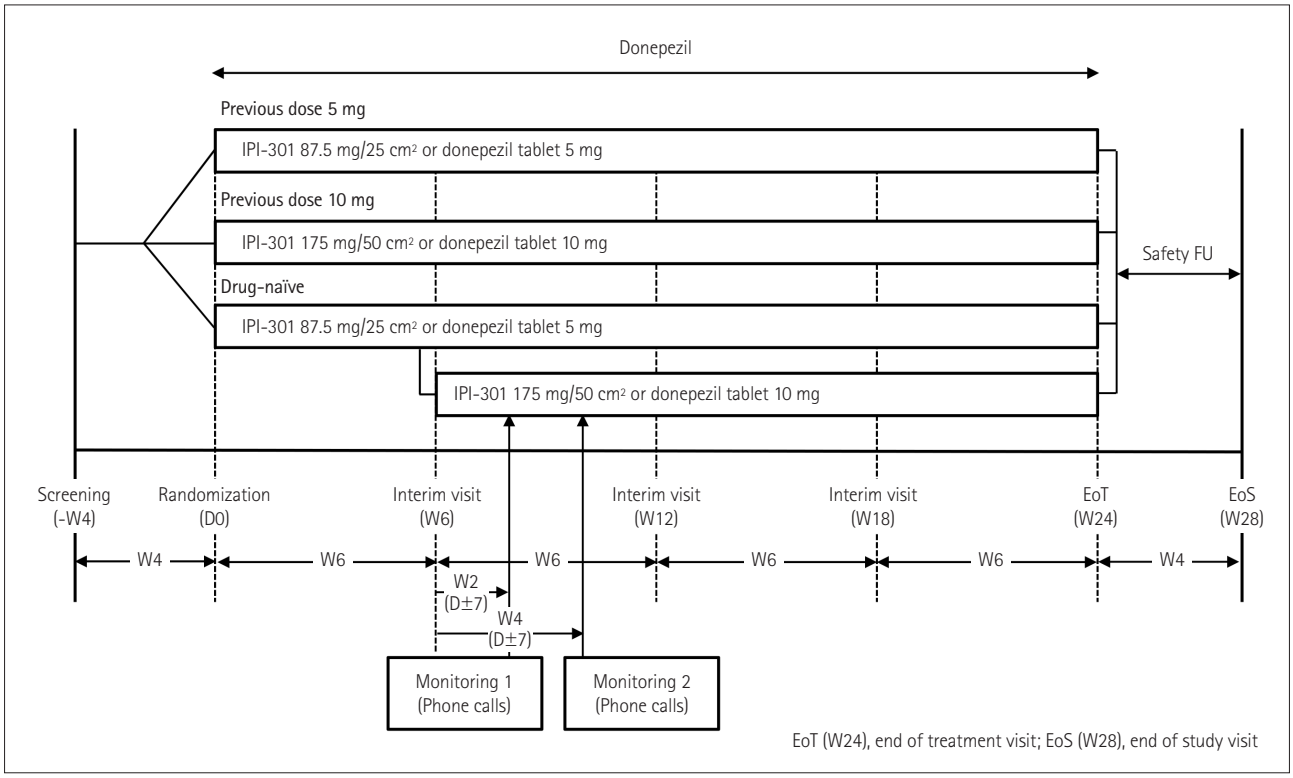

Fig. 1. Clinical protocol of the study.

brovascular disease, structural or developmental anomaly, epilepsy, or communicable, degenerative, or infectious/demyelinating central nervous system conditions) as the cause of dementia (e.g., more than three lacunar infarcts larger than 10 mm each, or severe white-matter disease equaling an evaluation rating of 3 on the Age-Related White Matter Changes scale); any severe or unstable medical disease that could interfere with the patient participating in any processes of the study (e.g, severe pulmonary, cardiovascular, gastrointestinal, hematological, endocrine, hepatic, or renal disease); and antidementia drug treatment with other than donepezil (galantamine, rivastigmine, and/or memantine) within 3 months prior to the date that informed consent was provided. Written informed consent was obtained from each patient prior to study initiation. Patients were considered eligible if they had voluntarily consented to participate in the clinical trial, met the inclusion criteria, and did not have of the exclusion criteria. All patients underwent medical history assessments, physical examinations, clinical laboratory tests, and other assessments at screening within 4 weeks prior to the first treatment administration (day 1). However, if a previous neuroimaging (MRI or nonenhanced CT) result within the previous 12 months was not available for review, an extended screening period of up to 6 weeks (i.e., 42 days prior to day 0) was permitted for the patient, in which they underwent MRI or nonenhanced CT. The study was conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice. The institutional review board of each hospital approved the protocol and consent forms prior to study initiation.

Outcome measures and safety

The primary objective of this trial was to determine the noninferiority of IPI-301 transdermal patch relative to oral donepezil tablets after 24 weeks of treatment in patients with mild-to-moderate AD by assessing cognitive function improvements based on the ADAS-Cog. Secondary efficacy endpoints were as follows: the CIBIC-Plus score at the end of dosing (week 24), the change in MMSE score after 24 weeks of treatment (compared to screening [prior to week 4]), the change in ADCS-ADL score after 24 weeks of treatment (compared with baseline [day 0]), and NPI score improvement after 24 weeks of treatment (compared with baseline [day 0]). The changes in degree (frequency×severity) and the amount of change in the total score for suffering experienced by the caregiver were evaluated. The changes in global CDR and CDR–Sum of Box (CDR-SOB) scores after 24 weeks of treatment (compared with 4 weeks prior) were also included in the assessment. Safety was followed up until 4 weeks after administration of the last dose. At the end of each visit, medical examinations (interviews, physical examinations, vital-sign checkups, C-SSRS score, and clinical laboratory tests) were performed in accor-

dance with the planned study timeline.

Sample size and randomization

In this clinical trial, 376 patients were randomly assigned to the two groups to ensure recruitment of at least 131 patients in each, considering a possible 30% dropout rate. The criterion for noninferiority in this study was evaluated based on the change in ADAS-Cog score as the primary endpoint, with the statistical power of the test set at 83%. The sample size calculated based on a significance level (α) of 0.025 (one-sided), an allocation ratio of study samples between the two groups (λ) of 1, and a noninferiority margin was 2.02 (lower limit of the 95% confidence interval [CI] based on a previous meta-analysis).

Statistical analysis

The data obtained in this clinical trial were analyzed in both a per-protocol set (PPS) and full-analysis set (FAS). The safety data were analyzed in the safety set. PPS analysis was regarded as the main analysis in this clinical trial. The primary endpoint in this trial was noninferiority of IPI-301, defined as a two-sided 95% CI upper bound for the difference between the IPI-301 and donepezil tablet (control) groups of <2.02 regarding the ADAS-Cog score change after 24 weeks of treatment compared with baseline (day 0). Between-group comparisons of continuous data were performed using paired *t*-tests or Wilcoxon rank-sum tests. These tests were also used to assess within-group differences. Pearson's chi-squared or Fisher's exact tests were used to examine differences in categorical data. Any missing values that arose during the primary efficacy evaluation after treatment were corrected. However, raw data were used in the secondary efficacy and safety evaluations without missing-value corrections. All analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA), and $p<0.05$ was considered significant in all analyses.

RESULTS

Baseline demographics

In total, 498 patients were initially screened for inclusion in the trial. Among the 399 patients remaining after excluding 99 patients, 303 (75.9%) completed the trial. Overall, 96 patients (24.1%) were withdrawn or dropped out during the clinical trial: 33 (8.3%) experienced safety-related acute reactions, 9 (2.3%) experienced serious AEs and adverse drug reactions, 32 (8.0%) withdrew consent, 12 (3.0%) had other reasons, and 10 (2.5%) violated eligibility criteria. The patients included in the FAS consisted of 159 males (42.6%) and 214 females (57.4%) aged 73.07±7.30 years (mean±SD). Regarding previous donepezil use and dosages used as stratification factors during patient recruitment, 219 (58.7%) and 62 (16.6%) patients had received doses of 10 and 5 mg/day, respectively, and 92 patients (24.7%) were naïve. The safety set included 393 (98.5%) of the 399 randomized patients: 195 (98.0%) and 198 (99.0%) in the IPI-301 and donepezil tablet control groups, respectively. The FAS included 373 patients (93.5%): 183 (92.0%) and 190 (95.0%) in the IPI-301 and donepezil tablet control groups, respectively. The PPS included 257 patients (64.4%): 119 (59.8%) and 138 (69.0%) in the IPI-301 and donepezil tab-

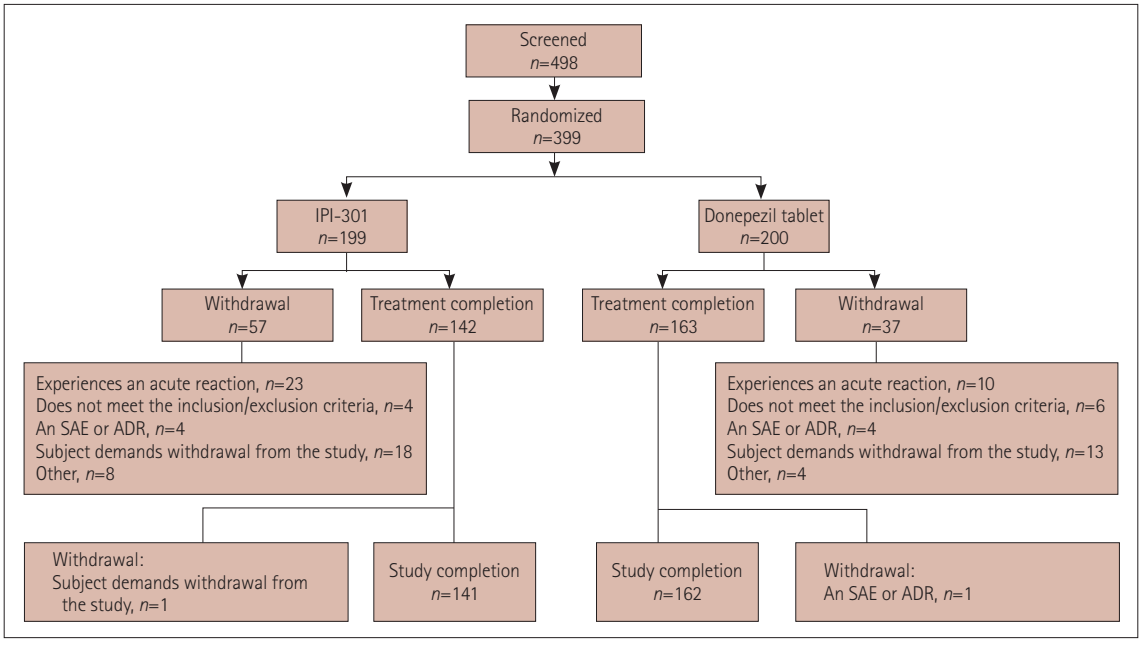

Fig. 2. Sample flowchart of participant inclusion throughout the trial. ADR, adverse drug reaction; SAE, serious adverse event.

let control groups, respectively (Fig. 2). Ages, sex ratios, previous donepezil use or dosages used, and racial profiles did not differ significantly between the two groups (Table 1).

Efficacy and safety

The primary objective of the present trial was to determine the noninferiority of IPI-301 donepezil transdermal patches relative to donepezil tablets after 24 weeks of treatment in patients with mild-to-moderate AD by assessing cognitive function improvements based on the ADAS-Cog. PPS analysis indicated that there were no significant differences in the changes of ADAS-Cog score at week 24 between the IPI-301 and donepezil tablet control groups compared with baseline (-0.47±5.74 vs. -0.93±4.89, p=0.8975) (Table 2). There was also a difference—quantified as the Hodges–Lehmann estimate of location shift—of 0.00 (95% CI: -1.00 to 1.33) between the IPI-301 and donepezil tablet control groups. Noninferiority was established as the upper bound of the 95% CI of the difference (<2.02) (Fig. 3). PPS analysis of the secondary outcome measures indicated that there were no significant differences between the two groups in the change in MMSE scores at week 24 compared with baseline (p=0.7018). PPS analysis also indicated that there were no significant differences between the two groups in CIBI-Plus scores at baseline (day 0) or CIBIC-Plus scores after 24 weeks of treatment (p=0.6974 and p=0.9097, respectively), in the changes in NPI intensity and caregiver suffering scores at week 24 compared with baseline (p=0.7656 and p=0.3433, respectively), or in the changes in global CDR score at weeks 12 and 24 compared with baseline (p=0.5417 and p=0.9990, respectively). The changes in CDR-SOB score at weeks 12 and 24, compared with baseline, also did not differ significantly between the two groups (p=0.9947 and p=0.9520, respectively).

PPS analysis indicated that there were no significant differences between the two groups in the changes in ADCS-ADL score at week 12 compared with baseline (p=0.1924). The change in ADCS-ADL score at week 24, compared with baseline, differed significantly between the two groups (p=0.0200)

Table 1. Demographics and baseline characteristics (full-analysis set)

	IPI-301 (n=183)	Donepezil tablet (n=190)	p	Total (n=373)
Age (yr)			0.6059*	
Mean±SD	72.90±7.12	73.24±7.49		73.07±7.30
Median (min, max)	73.00 (52.00, 85.00)	74.00 (55.00, 85.00)		74.00 (52.00, 85.00)
Sex, n (%)			0.8328†	
Male	77 (42.08)	82 (43.16)		159 (42.63)
Female	106 (57.92)	108 (56.84)		214 (57.37)
Ethnicity, n (%)			-	
Hispanic or Latino	0 (0)	0 (0)		0 (0)
Not Hispanic or Latino	181 (98.91)	186 (97.89)		367 (98.39)
Not reported	2 (1.09)	4 (2.11)		6 (1.61)
Unknown	0 (0)	0 (0)		0 (0)
Race, n (%)			0.7372†	
American Indian or Alaskan native	0 (0)	0 (0)		0 (0)
Asian	171 (93.44)	174 (91.58)		345 (92.49)
Black or African American	0 (0)	0 (0)		0 (0)
Native Hawaiian or other Pacific islander	0 (0)	0 (0)		0 (0)
White	12 (6.56)	14 (7.37)		26 (6.97)
Not reported	0 (0)	2 (1.05)		2 (0.54)
MMSE			0.3799*	
Mean±SD	18.87±4.23	19.20±4.29		19.04±4.25
Median (min, max)	19.00 (10.00, 26.00)	20.00 (10.00, 26.00)		19.00 (10.00, 26.00)
Global CDR scores			0.7980*	
Mean±SD	0.92±0.50	0.88±0.44		0.90±0.47
Median (min, max)	1.00 (0.50, 2.00)	1.00 (0.50, 2.00)		1.00 (0.50, 2.00)
CDR sum of box scores			0.5987*	
Mean±SD	5.21±2.84	4.96±2.56		5.08±2.70
Median (min, max)	4.50 (0.50, 14.00)	4.50 (0.50, 14.00)		4.50 (0.50, 14.00)

*Wilcoxon rank-sum test; †chi-square test.
CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

Table 2. Changes from baseline at week 24 for primary efficacy measures (Alzheimer's Disease Assessment Scale–Cognitive score, per-protocol set)

	IPI-301 (*n*=119)		Donepezil Tablet (*n*=138)	
	Mean±SD	Median (min, max)	Mean±SD	Median (min, max)
Baseline (day 0)	25.13±8.77	23.67 (6.67, 54.00)	23.93±7.38	23.5 (6.67, 43.00)
Week 24	24.66±10.37	23 (8.00, 62.00)	23.00±8.41	23.33 (6.66, 49.67)
Change from baseline to week 24	-0.47±5.74	-0.33 (-15.33, 25.00)	-0.93±4.89	-1 (-17.00, 17.33)

Hodges-Lehmann estimation-location shift (IPI-301 - Donepezil tablet): 0.00 (95% CI, -100 to 1.33), p=0.8975. If the upper limit of 95% two-sided CI <2.02 (noninferiority margin), test group is not inferior to the control group. Assumption of normality is rejected. Nevertheless, parametric method=treatment difference (95% CI) =0.46* (-0.85, 1.76), p=0.4911* (*t-test).
ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive.

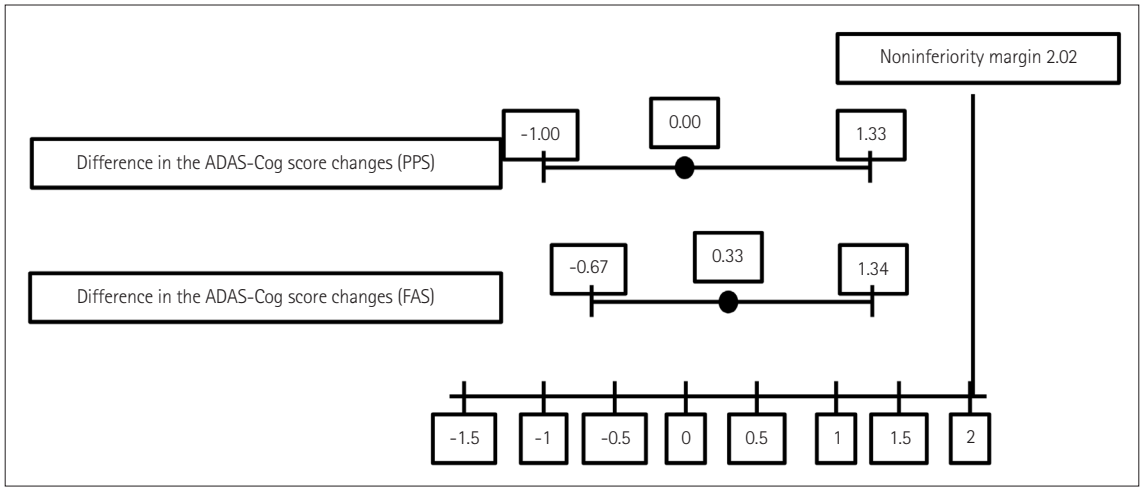

Fig. 3. Effect of IPI-301 (donepezil transdermal patch) on Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog) scores in patients with mild-to-moderate probable Alzheimer's disease (AD). The change in the ADAS-Cog score from baseline to 24 weeks was considered the primary endpoint. In both the per-protocol set (PPS) and full-analysis set (FAS), the patients assigned to the IPI-301 group experienced similar effects to the control group (donepezil tablets) from the baseline scores at week 24 (95% two-sided confidence interval upper bound for the difference of <2.02).

(Table 3). However, the subgroup analysis of changes in the full-itemized ADCS-ADL score excluding missing individual values at week 24 indicated that there was no significant difference between the two groups. Results of the full-itemized ADCS-ADL "improvement" responder analysis (involving patients with less-than-maximal functionality at baseline, but who improved during the study course) are provided in Supplementary Fig. 1 (in the online-only Data Supplement). The amounts and percentages of patients who experienced AEs are listed in Table 4. Serious adverse drug reactions and deaths only occurred in the donepezil tablet control group. However, the IPI-301 group presented significantly more local treatment-emergent AEs (TEAEs) such as pruritus or erythema compared with the control group. There were 36 TEAEs in 27 patients (13.85%) and 19 in 12 patients (6.06%) that led to early study termination in the IPI-301 and donepezil tablet control groups, respectively. Specifically, pruritus occurred in 10 patients (5.13%, 10 events) in the IPI-301 group and in 1 (0.51%, 1 event) in the donepezil tablet control group. Erythema occurred in four patients (2.05%, four events) in the IPI-301 group and in one (0.51%, one event) in the control group. Therefore, two types of events, pruritus or erythema, led to the difference in TEAE incidence that resulted in withdrawal from the trial between the two groups, which constituted 12 of the 15 events. The score for the C-SSRS, a subindicator questionnaire that assesses suicide risk, did not increase compared with baseline in either group during the study period.

DISCUSSION

Donepezil is a well-known reversible noncompetitive cholinesterase inhibitor that is used worldwide to treat cognitive symptoms in patients with mild-to-severe AD.[24,25] The most commonly used cholinesterase inhibitor formulations are currently oral tablets. However, oral cholinesterase inhibitors frequently induce adverse effects, such as gastrointestinal disorders and hepatic dysfunction caused by elevated peripheral acetylcholine levels.[5,26] In comparison with oral formulations, patch formulations can reduce the maximum systemic drug concentration by decreasing the absorption rate, leading to a reduced dosing frequency and to improving treatment compliance. The present 24-week, multinational, multicenter,

Table 3. Changes from baseline at week 24 for secondary efficacy measures (per-protocol set)

Outcome measures	Changes from baseline at week 24		
	IPI-301 (*n*=119)	Donepezil tablet (*n*=138)	*p**
CIBIC-plus	4.15±0.91, 4.00	4.11±0.86, 4.00	0.9097
MMSE	-0.55±2.49, 0.00	-0.40±2.32, 0.00	0.7018
ADCS-ADL	-3.06±8.11, -2.00	-1.05±6.96, 0.00	0.0200
Total score of intensity	-2.16±8.96, -1.00	-1.66±8.69, -1.00	0.7656
Total score of distress felt by the caregivers	-1.78±4.34, -1.00	-1.06±5.36, 0.00	0.3433
Global CDR Scores	0.05±0.28, 0.00	0.06±0.26, 0.00	0.9990
CDR sum of Box Scores	0.47±1.33, 0.00	0.38±1.35, 0.00	0.9520

Values are presented as mean±SD, median.
*Wilcoxon rank-sum test.
ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities Daily Living; CDR, Clinical Dementia Rating; CIBIC-plus, Clinician Interview-Based Impression of Change, plus caregiver interview; MMSE, Mini-Mental State Examination.

Table 4. Summary of adverse events observed during the clinical trial

Advers events	IPI-301 (*n*=195)		Donepezil tablet (*n*=198)		*p*
	n (%)	Events (95% CIs)	*n* (%)	Events (95% CIs)	
Pretreatment AEs	13 (6.67)	17 (3.17, 10.17)	16 (8.08)	18 (4.28, 11.88)	0.5919*
Total TEAEs	129 (66.15)	396 (59.51, 72.80)	115 (58.08)	333 (51.21, 64.95)	0.0991*
Total local TEAEs	78 (40.00)	132 (33.12, 46.88)	38 (19.19)	79 (13.71, 24.68)	<0.0001*
Total SAEs	16 (8.21)	18 (4.35, 12.06)	15 (7.58)	17 (3.89, 11.26)	0.8170*
Total SADRs	-	-	3 (1.52)	3 (0.00, 3.22)	0.2481†
Total treatment-related TEAEs	87 (44.62)	186 (37.64, 51.59)	56 (28.28)	143 (22.01, 34.56)	0.0008*
Total TEAEs that led to study withdrawal	27 (13.85)	36 (9.00, 18.69)	12 (6.06)	19 (2.74, 9.38)	0.0098*
Total deaths	-	-	2 (1.01)	2 (0.00, 2.40)	0.4988†

*Chi-square test; †Fisher's exact test.
AEs, adverse events; SADR, serious adverse drug reactions; SAEs, serious adverse events; TEAEs, treatment emergent adverse events.

randomized, double-blind, prospective clinical trial was performed to determine the efficacy and safety of a novel donepezil transdermal patch formulation, IPI-301, in comparison to the standard donepezil tablet formulation as a control. The percentages of patients with ≥80% treatment compliance in the FAS were 89.81% and 88.74% for the IPI-301 and donepezil tablet control groups, respectively, indicating that overall treatment compliance was favorable.

This study found no significant difference in the change in ADAS-Cog between the two groups with noninferiority in the main analysis set (PPS) and in the FAS. The clinical benefit of applying an IPI-301 donepezil transdermal patch twice weekly in maintaining cognitive function was therefore similar to that for daily treatment with donepezil tablet. The IPI-301 donepezil transdermal patch was suitable for use in patients who experienced difficulty in oral administration, and had a similar efficacy. We also observed that the ADCS-ADL score after 24 weeks was slightly lower in the IPI-301 group than in the control group. However, subgroup analysis according to each individual factor of ADCS-ADL indicated that there was no significant difference between the two groups (Supplementary Fig. 1 in the online-only Data Supplement). We therefore suggest that IPI-301 had no meaningful influence on the activities of daily living compared with the control. Notably, there were no significant differences in other secondary outcome measures (NPI, CIBIC-Plus, MMSE, CDR-SOB scores) between the IPI-301 and control groups compared with baseline. Among the 399 randomized patients, 393 (98.5%) were included in the safety set: 195 (98.0%) and 198 patients (99.0%) in the IPI-301 and donepezil tablet control groups, respectively. Evaluations of AEs, vital signs, and laboratory test results (e.g., hematology, blood chemistry, and urinalysis) indicated that the safety of the IPI-301 donepezil transdermal patch did not differ from that of oral donepezil tablets. Serious adverse drug reaction or death cases were only reported in the control group, but the rates of local TEAEs, including pruritus and erythema, were higher in the IPI-301 group. In particular, most events responsible for the significant intergroup difference in TEAEs leading to withdrawal from the trial were caused by pruritus or erythema (12 of 15 events).

A previous clinical trial found that switching from oral rivastigmine to transdermal rivastigmine patch was safe and tolerable in patients with AD, despite an increased incidence of skin reactions (e.g., itching and erythema).[27] Pruritus and erythema are subjective and objective symptoms, respectively, that can easily be recognized without the need for any partic-

ular diagnostic tool. IPI-301 was generally well-tolerated, as indicated by the mild severity of most TEAEs; the few serious AEs in this study all occurred in the control group. IPI-301 is a new patch formulation that can reduce the maximum systemic drug concentration by decreasing the absorption rate, leading to reduced dosing frequency and improved treatment compliance. Previously reported pharmacokinetic analyses of IPI-301 predicted that a 175-mg donepezil patch applied at 72- and 96-h intervals would have similar concentration profiles to oral dosing with 10 mg of donepezil at a 24-h interval, while an 87.5-mg patch applied at 72- and 96-h intervals would be similar to oral dosing with 5 mg of donepezil at a 24-h interval.[28] Previous studies found that the mean concentration and 72-h area under the curve in the steady state were slightly higher for patch regimens than for the corresponding oral dosing regimens; the plasma concentration over time was much more stable in each individual after applying the patch formulation than after oral administration.[29] The pharmacokinetic mechanism of IPI-301 is presumed to maintain stable clinical effects even if applied twice weekly. Moreover, the slower increase in its plasma concentration is known to reduce AEs, while the higher C_{max} and sustained efficacy may increase cognitive benefits.[12,30] IPI-301 may therefore be a useful new alternative that can address needs arising from patient preferences or health conditions, including gastrointestinal disorders and liver diseases; it can also aid in treating patients who experience difficulty in taking oral medications, when applied with symptom monitoring after patch application (for pruritus), application-site examinations (e.g., for erythema), patch hypersensitivity reaction history evaluations, and appropriate medication counseling. On the basis of the above points, IPI-301 is considered noninferior to an existing donepezil preparation for oral use in patients with mild-to-moderate AD regarding the efficacy of cognitive function improvement, as assessed by the ADAS-Cog, and it has a favorable safety profile.

In conclusion, a novel donepezil transdermal patch formulation, IPI-301, was safe and efficacious for patients with mild-to-moderate AD when compared with oral donepezil. Based on the results of this study, IPI-301 can be recommended for patients with mild-to-moderate AD who experience hypersensitivity reactions during oral donepezil formulation treatment and for patients who have swallowing difficulties or refuse to take oral medications.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.4.428.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Hyun Jeong Han https://orcid.org/0000-0002-1129-6340
Mee Young Park https://orcid.org/0000-0002-5683-1634
Kyung Won Park https://orcid.org/0000- 0002-6788-5267
Kee Hyung Park https://orcid.org/0000-0001-6847-6679
Seong Hye Choi https://orcid.org/0000-0002-4180-8626
Hee-Jin Kim https://orcid.org/0000-0001-7880-690X
Dong Won Yang https://orcid.org/0000-0002-4733-7298
Esther Gunaseli A/P M. Ebenezer https://orcid.org/0000-0003-4948-3368
Yuan-Han Yang https://orcid.org/0000-0002-1918-9021
Gurudev M. Kewalram https://orcid.org/0000-0002-5137-7313
Seol-Heui Han https://orcid.org/0000-0003-3608-2514

Author Contributions

Conceptualization: Seong Hye Choi. Data curation: Mee Young Park, Kyung Won Park, Kee Hyung Park, Seong Hye Choi, Hee-Jin Kim, Dong Won Yang, Esther Gunaseli A/P M. Ebenezer, Yuan-Han Yang, Gurudev M. Kewalram. Methodology: Seol-Heui Han. Project administration: Mee Young Park, Kyung Won Park. Supervision: Seol-Heui Han. Writing—original draft: Hyun Jeong Han. Writing—review & editing: Hyun Jeong Han.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This clinical trial was supported by the iCure Pharmaceutical Incorporated, Seoul, Republic of Korea

Acknowledgements

The authors would like to acknowledge the commitment and research work of additional IPI-301 Study Group: Jae-Hong Lee, Asan Medical Center, Seoul; Dong Won Yang, The Catholic University of Korea, Seoul St Mary's Hospital, Seoul; Sang Won Seo, Samsung Medical Center, Seoul; Kun-Woo Park, Korea University Anam Hospital, Seoul; Min Ju Kang, Veterans Health Service Medical Center, Seoul; Soo Jin Yoon, Eulji University Hospital, Daejeon; Byeong Chae Kim, Chonnam National University Hospital, Gwangju; GeonHa Ki, Ewha Womans University Medical Center, Seoul; Young Chul Youn, Chung-Ang University Hospital, Seoul; Seong-Ho Koh, Hanyang University Guri Hospital, Guri; So Young Moon, Ajou University Medical Center, Suwon; Hyon-Ah Yi, Keimyung University Dongsan Medical Center, Daegu; Ae Young Lee, Chungnam National University Hospital, Daejeon; YoungSoo Shim, Bucheon St Mary's Hospital, Bucheon; Jun Hong Lee, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea. Chin-Chang Huang, Chang Gung Memorial Hospital, Taoyuan; Ming-Chyi Pai, National Cheng Kung University Hospital, Tainan; Ta-Fu Chen, National Taiwan University Hospital, Taipei; Chung-Hsiang Liu, China Medical University Hospital, Taichung; Wen-Fu Wang, Changhua Christian Medical Foundation Changhua Christian Hospital, Changhua; Chaur-Jong Hu, Taipei Medical University Shuang Ho Hospital, New Taipei; Ming-Hsiu Wu, Chi-Mei Hospital, Tainan; Chin-I Chen, Taipei Municipal Wan Fang Hospital, Taipei; Yu Sun, En Chu Kong Hospital of The Hsing Tian Kong Foundation Medical Mission, New Taipei; Wen-Neng Chang, Chang Gung Medical Foundation Kaohsiung Chang Gung Memorial Hospita, Kaohsiung; Ting-Bin Chen, Taichung Veterans General Hospital, Taichung, Taiwan. Suraya Binti Yusoff, Hospital Sultan Ismail, Johor; Chin Loi Fei, Hospital Tengku Ampuan Rahimah, Selangor; Cheah Wee Kooi, Hospital Taiping, Perak, Malaysia. Henry Zeimer, Austin Health, Heidelberg; Rosalyn Lai, KaRa Institute of Neurological Diseases Pty Ltd, Macquarie Park; Susan Kurrle, Hornsby Ku-Ring-Gai Hospital, Hornsby; Bruce Brew, St Vincent's Hospital Sydney Limited, Darlinghurst; Peter Farnbach, Neuro Trials Vic-

toria Pty Ltd, Noble Park; Andrew Gleason, Caulfield Hospital, Caulfield; Peter Schofield, HNE Calvary Mater Newcastle Hospital, Waratah, Australia.

REFERENCES

1. Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH, et al. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997;278:1363-1371.
2. Patterson C. *World Alzheimer Report 2018. The State of the Art of Dementia Research: New Frontiers.* London: Alzheimer's Disease International, 2018.
3. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 1998;50:136-145.
4. Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, et al. Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial. *Arch Neurol* 2004;61:1852-1856.
5. Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. *Int J Clin Pract Suppl* 2002;127:45-63.
6. Cummings JL, Geldmacher D, Farlow M, Sabbagh M, Christensen D, Betz P. High-dose donepezil (23 mg/day) for the treatment of moderate and severe Alzheimer's disease: drug profile and clinical guidelines. *CNS Neurosci Ther* 2013;19:294-301.
7. Lee C, Lee K, Yu H, Ryu SH, Moon SW, Han C, et al. Adverse events with sustained-release donepezil in Alzheimer disease: relation to body mass index. *J Clin Psychopharmacol* 2017;37:401-404.
8. Mauskopf JA, Paramore C, Lee WC, Snyder EH. Drug persistency patterns for patients treated with rivastigmine or donepezil in usual care settings. *J Manag Care Pharm* 2005;11:231-251.
9. Utsuki T, Uchimura N, Irikura M, Moriuchi H, Holloway HW, Yu QS, et al. Preclinical investigation of the topical administration of phenserine: transdermal flux, cholinesterase inhibition, and cognitive efficacy. *J Pharmacol Exp Ther* 2007;321:353-361.
10. Winblad B, Machado JC. Use of rivastigmine transdermal patch in the treatment of Alzheimer's disease. *Expert Opin Drug Deliv* 2008;5:1377-1386.
11. Priano L, Gasco MR, Mauro A. Transdermal treatment options for neurological disorders: impact on the elderly. *Drugs Aging* 2006;23:357-375.
12. Bhowmik D, Chiranjib BD, Chandira M, Jayakar B, Sampath KP. Recent advances in transdermal drug delivery system. *Int J Pharm Tech Res* 2010;2:68-77.
13. Oertel W, Ross JS, Eggert K, Adler G. Rationale for transdermal drug administration in Alzheimer disease. *Neurology* 2007;69(4 Suppl 1):S4-S9.
14. Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S13-S21.
15. Reisberg B, Schneider L, Doody R, Anand R, Feldman H, Haraguchi H, et al. Clinical global measures of dementia. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 3:8-18.
16. Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11:S33-S39.
17. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308-2314.
18. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011;168:1266-1277.
19. Cooper J. Diagnostic and statistical manual of mental disorders (4th edn, text revision) (DSM–IV–TR) Washington, DC: American Psychiatric Association 2000. *Br J Psychiatry* 2001;179:85.
20. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263-269.
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
22. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412-2414.
23. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-260.
24. Dooley M, Lamb HM. Donepezil: a review of its use in Alzheimer's disease. *Drugs Aging* 2000;16:199-226.
25. Hong YJ, Han HJ, Youn YC, Park KW, Yang DW, Kim S, et al. Safety and tolerability of donepezil 23 mg with or without intermediate dose titration in patients with Alzheimer's disease taking donepezil 10 mg: a multicenter, randomized, open-label, parallel-design, three-arm, prospective trial. *Alzheimers Res Ther* 2019;11:37.
26. Dunn NR, Pearce GL, Shakir SA. Adverse effects associated with the use of donepezil in general practice in England. *J Psychopharmacol* 2000;14:406-408
27. Han HJ, Lee JJ, Park SA, Park HY, Kim JE, Shim YS, et al. Efficacy and safety of switching from oral cholinesterase inhibitors to the rivastigmine transdermal patch in patients with probable Alzheimer's disease. *J Clin Neurol* 2011;7:137-142.
28. Kim YH, Choi HY, Lim HS, Lee SH, Jeon HS, Hong D, et al. Single dose pharmacokinetics of the novel transdermal donepezil patch in healthy volunteers. *Drug Des Devel Ther* 2015;9:1419-1426.
29. Yoon SK, Bae KS, Hong DH, Kim SS, Choi YK, Lim HS. Pharmacokinetic evaluation by modeling and simulation analysis of a donepezil patch formulation in healthy male volunteers. *Drug Des Devel Ther* 2020;14:1729-1737.
30. Sozio P, Cerasa LS, Marinelli L, Di Stefano A. Transdermal donepezil on the treatment of Alzheimer's disease. *Neuropsychiatr Dis Treat* 2012;8:361-368.