Dement Neurocogn Disord. 2023 Jul;22(3):100-108
https://doi.org/10.12779/dnd.2023.22.3.100
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Original Article

Effects of GV1001 on Language Dysfunction in Patients With Moderate-to-Severe Alzheimer's Disease: *Post Hoc* Analysis of Severe Impairment Battery Subscales

Hyuk Sung Kwon[1] **Seong-Ho Koh**[1,2] **Seong Hye Choi**[3] **Jee Hyang Jeong**[4] **Hae Ri Na**[5] **Chan Nyoung Lee**[6] **YoungSoon Yang**[7] **Ae Young Lee**[8] **Jae-Hong Lee**[9] **Kyung Won Park**[10] **Hyun Jeong Han**[11] **Byeong C. Kim**[12] **Jinse Park**[13] **Jee-Young Lee**[14] **Kyu-Yong Lee**[1] **Sangjae Kim**[15]

[1]Department of Neurology, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea
[2]Department of Translational Medicine, Hanyang University Graduate School of Biomedical Science & Engineering, Seoul, Korea
[3]Department of Neurology, Inha University School of Medicine, Incheon, Korea
[4]Department of Neurology, Ewha Womans University College of Medicine, Seoul, Korea
[5]Department of Neurology, Bobath Memorial Hospital, Seongnam, Korea
[6]Department of Neurology, Korea University Anam Hospital, Seoul, Korea
[7]Department of Neurology, Soonchunhyang University Cheonan Hospital, Cheonan, Korea
[8]Department of Neurology, Chungnam National University Hospital, Daejeon, Korea
[9]Department of Neurology, Asan Medical Center, Seoul, Korea
[10]Department of Neurology, Dong-A University Hospital, Busan, Korea
[11]Department of Neurology, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea
[12]Department of Neurology, Chonnam National University Medical School and Hospital, Gwangju, Korea
[13]Department of Neurology, Haeundae Paik Hospital, Inje University, Buasn, Korea
[14]Department of Neurology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea
[15]Teloid Inc., Los Angeles, CA, USA

Received: Jun 15, 2023
Accepted: Jun 22, 2023
Published online: Jul 11, 2023

Correspondence to
Seong-Ho Koh
Department of Neurology, Hanyang University Guri Hospital, Hanyang University College of Medicine, 153 Gyeongchun-ro, Guri 11923, Korea.
Email: ksh213@hanyang.ac.kr

Sangjae Kim
Teloid Inc., 3580 Wilshire Boulevard, Suite 900-31, Los Angeles, CA 90010, USA.
Email: chiron@gemvax.com

ORCID iDs
Hyuk Sung Kwon
https://orcid.org/0000-0002-2005-0983
Seong-Ho Koh
https://orcid.org/0000-0001-5419-5761
Seong Hye Choi
https://orcid.org/0000-0002-4180-8626
Jee Hyang Jeong
https://orcid.org/0000-0001-7945-6956
Hae Ri Na
https://orcid.org/0000-0002-3419-8428
Chan Nyoung Lee
https://orcid.org/0000-0002-1285-4658

ABSTRACT

Background and Purpose: The efficacy and safety of GV1001 have been demonstrated in patients with moderate-to-severe Alzheimer's disease (AD). In this study, we aimed to further demonstrate the effectiveness of GV1001 using subscales of the Severe Impairment Battery (SIB), which is a validated measure to assess cognitive function in patients with moderate-to-severe AD.
Methods: We performed a *post hoc* analysis of data from a 6 month, multicenter, phase 2, randomized, double-blind, placebo-controlled trial with GV1001 (ClinicalTrials.gov, NCT03184467). Patients were randomized to receive either GV1001 or a placebo for 24 weeks. In the current study, nine subscales of SIB—social interaction, memory, orientation, language, attention, praxis, visuospatial ability, construction, and orientation to name—were compared between the treatment (GV1001 1.12 mg) and placebo groups at weeks 12 and 24. The safety endpoints for these patients were also determined based on adverse events.
Results: In addition to the considerable beneficial effect of GV1001 on the SIB total score, GV1001 1.12 mg showed the most significant effect on language function at 24 weeks compared to placebo in both the full analysis set (FAS) and per-protocol set (PPS) (p=0.017

DND Dementia and Neurocognitive Disorder

YoungSoon Yang
https://orcid.org/0000-0002-2448-2599
Ae Young Lee
https://orcid.org/0000-0001-9790-0838
Jae-Hong Lee
https://orcid.org/0000-0001-7368-4560
Kyung Won Park
https://orcid.org/0000-0002-6788-5267
Hyun Jeong Han
https://orcid.org/0000-0002-1129-6340
Byeong C. Kim
https://orcid.org/0000-0001-6827-6730
Jinse Park
https://orcid.org/0000-0001-8738-5422
Jee-Young Lee
https://orcid.org/0000-0002-9120-2075
Kyu-Yong Lee
https://orcid.org/0000-0001-8855-7513
Sangjae Kim
https://orcid.org/0009-0003-8877-1060

Funding
This research was supported by grants from the Korea Dementia Research Center (KDRC) funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (HI20C0253, HU21C0113, and HU21C0007), and GemVax & Kael Co., Ltd.

Conflict of Interest
KSJ is an employer of GemVax & Kael Co., Ltd. and holds equity in the company. Other authors have no conflicts of interest to declare.

Author Contributions
Conceptualization: Koh SH, Kim S; Formal analysis: Kim S; Funding acquisition: Koh SH, Kim S; Investigation: Kwon HS, Koh SH, Choi SH, Jeong JH, Na HR, Lee CN, Yang Y, Lee AY, Lee JH, Park KW, Han HJ, Kim BC, Park J, Lee JY, Lee KY; Supervision: Choi SH, Jeong JH, Na HR, Lee CN, Yang Y, Lee AY, Lee JH, Park KW, Han HJ, Kim BC, Park J, Lee JY, Lee KY; Visualization: Kwon HS; Writing - original draft: Kwon HS; Writing - review & editing: Koh SH, Kim S.

and p=0.011, respectively). The rate of adverse events did not differ significantly between the 2 groups.
Conclusions: Patients with moderate-to-severe AD receiving GV1001 had greater language benefits than those receiving placebo, as measured using the SIB language subscale.

Keywords: GV1001; Efficacy; Alzheimer's Disease; Language

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, and its prevalence is increasing worldwide.[1,2] Acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine have been approved for the symptomatic treatment of AD.[3] Although the effects of these medications may last long, they are not considered to delay the progression of the disease.[4] Recently, anti-amyloid agents (aducanumab and lecanemab) have shown efficacy in treating the pathological change of early AD, and the United States Food and Drug Administration has approved them for the treatment of early AD.[5] However, treatment options for patients with moderate-to-severe AD are limited, leading to a significant unmet need.

GV1001 has been suggested to have diverse mode of action against AD, including anti-apoptotic, anti-inflammatory, anti-aging, anti-oxidant, and mitochondrial stabilizing effects.[6,7] The efficacy and safety of GV1001 1.12 mg in patients with moderate-to-severe AD was shown in phase 2 randomized clinical trial by analyzing the change in Severe Impairment Battery (SIB) scores over a duration of 24 weeks.[2] The SIB score is a reliable measure of cognitive function and disease progression in patients with moderate-to-severe AD, who may exhibit a "floor effect".[8,9] It consists of 9 subscales: social interaction, memory, orientation, language, attention, praxis, visuospatial ability, construction, and orientation to name. Among these subscales, the SIB-Language (SIB-L) subscale has the greatest proportion of items (24 of 51 total items), because of the importance of language.[10] These subscales, including SIB-L, have been used to evaluate the efficacy of acetylcholinesterase inhibitors and memantine in patients with moderate-to-severe AD in large prospective clinical trials.[11-14]

In the current study, our objective was to further demonstrate the efficacy of subcutaneous injection of GV1001 1.12 mg in moderate-to-severe AD, using SIB subscales. We conducted a *post hoc* analysis of our recent multicenter, randomized, double-blind clinical trial with GV1001.[2]

METHODS

Study design and post hoc analysis population

The clinical design and detailed methods used in the original clinical trial have been previously described.[2] In brief, this 24 week, multicenter, randomized, double-blind, placebo-controlled, prospective clinical trial included patients with moderate-to-severe AD (Mini-Mental State Examination [MMSE] ≤ 19, Global Deterioration Scale [GDS] score of 5–6, and receiving stable doses of donepezil at 10 mg/day ≥ 3 months before the screening visit). The primary efficacy endpoint was the change in SIB score from baseline to week 24. Patients with a GDS score of 7 were not assessed for eligibility, because due to the loss of linguistic and fundamental motor abilities, such as walking, they were unable to perform

https://doi.org/10.12779/dnd.2023.22.3.100

cognitive tests and follow the clinical trial protocol. Eligible patients were enrolled and randomly assigned in 1:1:1 ratios to GV1001 0.56 mg, GV1001 1.12 mg, and placebo (normal saline) groups. The study treatment was administered by subcutaneous (SC) injection every week for 4 weeks (4 times), followed by SC administration every 2 weeks until week 24 (10 times), for a total of 14 SC injections. Current *post hoc* analysis was performed in patients assigned to the GV1001 1.12 mg or placebo groups in both the full analysis set (FAS) and the per-protocol set (PPS).

Analysis of the effects on the subscales of SIB

The SIB includes 51 questions with scores ranging (0 to 100). It is divided into nine subscales (maximum score): social interaction (6), memory (14), orientation (6), language (46), attention (6), praxis (8), visuospatial ability (8), construction (4), and orientation to name (2). Safety endpoints were determined based on adverse events, laboratory test results, vital signs, and other safety-related observations. The χ^2 test and analysis of variance were used to assess baseline characteristics. Changes from baseline to weeks 12 and 24 in the SIB subscale scores for the GV1001 and placebo groups were analyzed using a mixed effects model for repeated measures (MMRM) analysis. For each endpoint, the least squares (LS) mean for each treatment group was calculated, along with the treatment-placebo differences (GV1001 vs. placebo), 95% confidence intervals (CIs) for differences, and the *p*-values for treatment-placebo differences. Comparisons between groups were performed using a 2-sided significance level of 0.05. All statistical analyses were performed using Stata version 18.0 (StataCorp LLC, College Station, TX, USA).

Ethics statement

The study protocol was approved by the independent Institutional Review Boards of Hanyang University of Guri Hospital (2017-03-019) and each participating center. The process was performed according to Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

RESULTS

A total of 96 participants were randomized between September 2017 and September 2019. In the current study, 28 participants assigned to the 1.12 mg GV1001 group, and 27 participants assigned to the placebo group were included and analyzed using FAS (**Fig. 1**). The PPS consisted of 25 participants in the GV1001 group, and 26 participants in the placebo group.

Baseline characteristics, including age, sex, age at AD diagnosis, years since diagnosis of AD, and total SIB, Korean version of MMSE, Clinical Dementia Rating-Sum of Boxes, Neuropsychiatric Inventory, GDS, Alzheimer's Disease Cooperative Study-Activities of Daily Living, and Clinician Interview-based Impression of Severity scores, were similar between the GV1001 and placebo groups (**Table 1**).

Regarding the total SIB score, **Table 2** demonstrates the significant benefit of GV1001 compared to placebo, in the FAS, at weeks 12 and 24 (p=0.031 and p=0.026, respectively), by comparing the LS mean change from baseline. This difference was statistically significant in the PPS (p=0.016 at week 12, and p=0.017 at week 24). Among the SIB subscales, language (p=0.017) and praxis (p=0.047) showed significant benefits for the mean change in LS from baseline in the FAS at week 24 (**Table 2**, **Fig. 2**). In PPS, this benefit was demonstrated only

https://doi.org/10.12779/dnd.2023.22.3.100

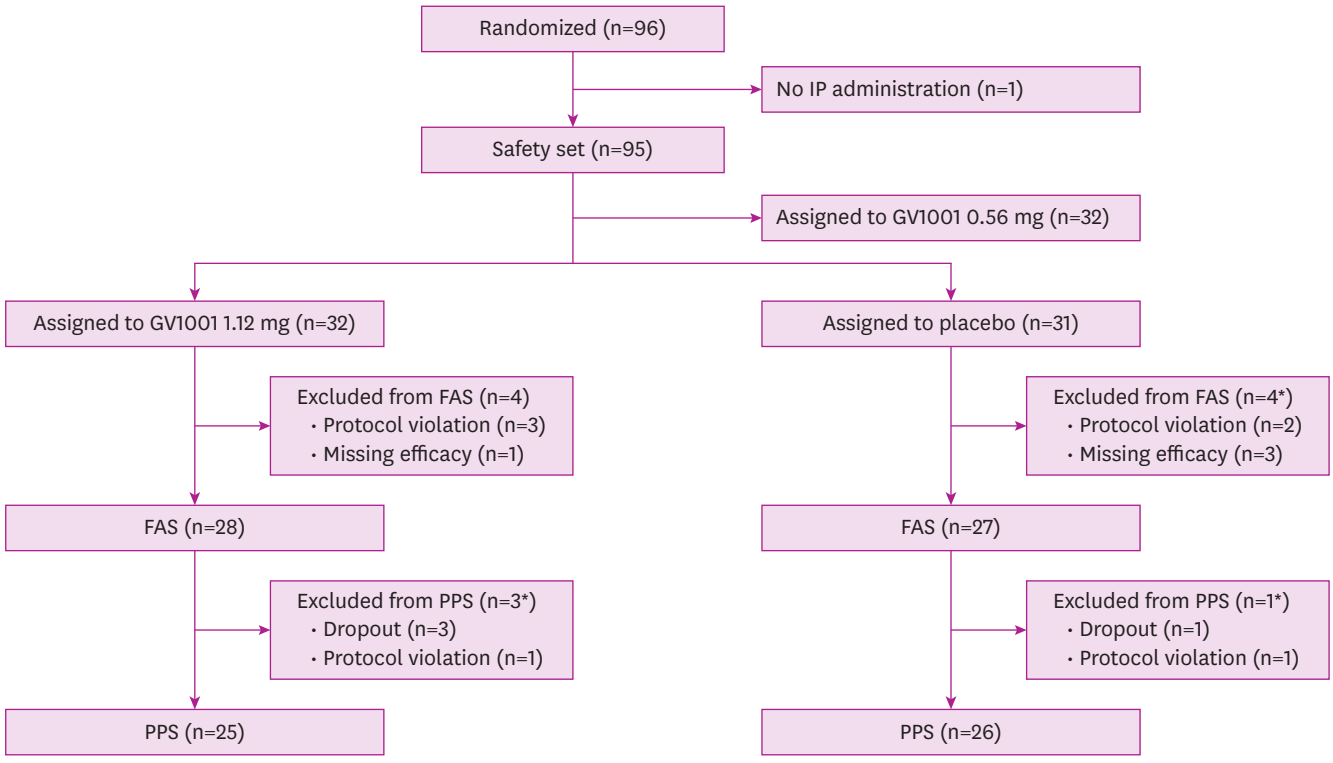

Fig. 1. Study profile.
Disposition of participants throughout the trial.
IP: investigational product, FAS: full analysis set, PPS: per-protocol set.
*One participant was excluded due to multiple reasons.

for language (p=0.011). At week 12, the mean change in LS from baseline, for memory, was significantly different between the GV1001 and placebo groups in FAS and PPS (p=0.037 and p=0.047, respectively).

Table 3 describes the number of treatment-emergent adverse events (TEAEs) in the study participants. There were no significant differences in TEAEs between the groups (**Table 3**). No severe TEAE was noted in the GV1001 1.12 mg group.

DISCUSSION

In this *post hoc* analysis, the significant beneficial effect of GV1001 on language in patients with moderate-to-severe AD was demonstrated using an SIB-L subscale. The benefits were evident in both FAS and PPS. The GV1001 1.12 mg treatment group showed either an improvement or no change in language function after 24 weeks. Among the patients in the GV1001 1.12 mg treatment group, only one patient showed more than 3.7 points decrement in the SIB-L score, which is considered a clinically relevant change.[12]

Language dysfunction is one of the most noticeable and problematic manifestations of AD.[15] As the stage of AD increases, the patient's language ability decreases. This causes enormous distress and burden for both patients and their caregivers, as they cannot communicate adequately and understand each other's needs.[16] Language also plays an important role

https://doi.org/10.12779/dnd.2023.22.3.100

Table 1. Demographic and baseline characteristics

Characteristics	GV1001 1.12 mg (n=32)	Placebo (n=31)	Overall (n=63)	*p*-value
Age (yr)				0.764*
Mean ± SD	71.6±8.4	70.9±8.9	71.3±8.6	
Median	75	72	74	
Min, Max	56.0, 82.0	56.0, 84.0	56.0, 84.0	
Sex				0.513†
Male	15 (46.9)	12 (38.7)	27 (42.9)	
Female	17 (53.1)	19 (61.3)	36 (57.1)	
Age at AD diagnosis (yr)				0.943*
Mean ± SD	67.8±8.4	67.9±8.6	67.9±8.4	
Median	70	68	68	
Min, Max	50.0, 80.0	54.0, 82.0	50.0, 82.0	
Years since diagnosis of AD				0.194*
Mean ± SD	4.4±2.6	3.6±1.7	4.0±2.2	
Median	4	3	4	
Min, Max	1.0, 10.0	1.0, 8.0	0.0, 10.0	
SIB, total				0.840*
Mean ± SD	76.9±20.1	75.9±16.5	76.4±18.2	
Median	84	81	82	
Min, Max	15.0, 96.0	39.0, 97.0	15.0, 97.0	
K-MMSE				0.552*
Mean ± SD	12.6±5.1	11.9±4.9	12.3±5.0	
Median	13	12	13	
Min, Max	1.0, 19.0	4.0, 19.0	1.0, 19.0	
CDR-SOB				0.979*
Mean ± SD	10.1±4.1	10.1±4.1	10.1±4.1	
Median	10	10	10	
Min, Max	5.0, 23.0	4.0, 18.0	4.0, 23.0	
NPI				0.370*
Mean ± SD	22.6±16.7	18.8±14.4	20.9±15.7	
Median	18	14	16.5	
Min, Max	4.0, 68.0	1.0, 63.0	1.0, 68.0	
GDS				0.726*
Mean ± SD	5.3±0.5	5.4±0.5	5.4±0.5	
Median	5	5	5	
Min, Max	5.0, 6.0	5.0, 6.0	5.0, 6.0	
ADCS-ADL				0.839*
Mean ± SD	35.8±10.3	32.9±9.9	34.3±10.1	
Median	35.5	33	34	
Min, Max	14.0, 51.0	12.0, 54.0	12.0, 54.0	
CIBIS				0.739*
Mean ± SD	4.8±0.8	4.7±0.9	4.8±0.8	
Median	5	5	5	
Min, Max	3.0, 6.0	3.0, 6.0	3.0, 6.0	

p-value for the differences between the GV1001 and placebo groups. Values are presented as number (%) not otherwise specified.
SD: standard deviation, AD: Alzheimer's disease, SIB: Severe Impairment Battery, K-MMSE, Korean version of Mini-Mental State Examination, CDR-SOB: Clinical Dementia Rating Scale-Sum of Boxes, NPI: Neuropsychiatric Inventory, GDS: Global Deterioration Scale, ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living, CIBIS: Clinician Interview-based Impression of Severity.
*Analysis of variance and †χ^2 test were used.

in maintaining emotional connection between the patient and their caregivers, including family.[10] Mortality was associated with lower verbal fluency,[17] and diverse neuropsychiatric symptoms (i.e., depression, agitation, and aggression) were caused by communication problems.[15] Language dysfunction also disturbs appropriate palliative care, including pain control.[18] These neuropsychiatric symptoms and uncontrolled pain can worsen the cognition and daily life activities of patients.[15,19] Therefore, treatment that can improve language function might reduce the problematic neuropsychiatric symptoms, and adequate pain

https://doi.org/10.12779/dnd.2023.22.3.100

Table 2. Effects of GV1001 on the total score of SIB and subscales in FAS and PPS

Variable	Week	LS mean of CFB (± SE)					
		FAS			PPS		
		GV1001 1.12 mg (n=28)	Placebo (n=27)	*p*-value	GV1001 1.12 mg (n=25)	Placebo (n=26)	*p*-value
SIB, total	12	0.74±1.42	−3.65±1.45*	0.031	1.00±1.49	−4.04±1.47*	0.016
	24	−0.33±2.11	−6.93±2.09*	0.026	−0.12±2.13	−7.23±2.09*	0.017
Social interaction	12	−0.29±0.15	−0.25±0.16	0.865	−0.11±0.16	0.11±0.15	0.317
	24	−0.1±0.22	−0.42±0.22	0.314	0.05±0.18	0.18±0.18	0.603
Memory	12	0.55±0.47	−0.85±0.48*	0.037	0.55±0.51	−0.88±0.5*	0.047
	24	0.24±0.53	−0.70±0.53	0.210	0.23±0.54	−0.72±0.53	0.210
Orientation	12	−0.02±0.18	−0.35±0.18	0.199	−0.01±0,19	−0.33±0.19	0.245
	24	0.14±0.22	−0.42±0.21	0.067	0.15±0.22	−0.41±0.22	0.074
Language	12	0.37±0.74	−1.31±0.75	0.111	0.48±0.79	−1.53±0.77	0.069
	24	0.04±0.98	−3.26±0.97*	0.017	0.12±1.00	−3.42±0.98*	0.011
Attention	12	0.04±0.25	−0.2±0.25	0.503	0.09±0.26	−0.28±0.25	0.304
	24	−0.34±0.28	−0.26±0.28	0.823	−0.31±0.28	−0.32±0.28	0.976
Praxis	12	0.09±0.2	−0.38±0.20	0.101	0.09±0.21	−0.36±0.2	0.121
	24	−0.19±0.27	−0.95±0.27*	0.047	−0.19±0.27	−0.93±0.27	0.050
Visuospatial ability	12	−0.01±0.26	−0.17±0.27	0.672	−0.01±0.29	−0.14±0.29	0.757
	24	0.19±0.38	−0.77±0.38	0.074	0.19±0.39	−0.76±0.38	0.083
Construction	12	−0.02±0.17	−0.08±0.17	0.792	−0.03±0.19	−0.12±0.18	0.740
	24	−0.19±0.18	−0.1±0.17	0.735	−0.19±0.18	−0.12±0.18	0.770
Orientation to name	12	0.04±0.06	−0.08±0.06	0.140	0.04±0.06	−0.08±0.06	0.150
	24	−0.08±0.07	−0.08±0.07	0.964	−0.08±0.07	−0.08±0.07	0.959

p-value for the differences between the GV1001 and placebo groups. The differences between the treatment and placebo groups were assessed using the mixed-effects model for repeated measures analysis.
SIB: Severe Impairment Battery, FAS: full analysis set, PPS: per-protocol set, LS: least square, CFB: change from baseline, SE: standard error.
*$p<0.05$.

Table 3. Overall summary of TEAEs by severity: safety set population

All TEAEs	Placebo (n=31)		GV1001 1.12 mg (n=32)		Overall (n=63)		*p*-value*	*p*-value†
	No. (%)*	Events†	No. (%)*	Events†	No. (%)	Events		
Mild	12 (38.7)	32	10 (31.3)	34	22 (34.9)	66	0.122	0.179
Moderate	2 (6.5)	4	5 (15.6)	10	7 (11.1)	14		
Severe	2 (6.5)	2	0 (0.0)	0	2 (3.2)	2		

The differences between the treatment group and placebo group were assessed using the χ^2 test.
TEAE: treatment-emergent adverse event.
**p*-value for the differences in the number of patients between the GV1001 and placebo groups.
†*p*-value for the differences in the number of events between the GV1001 and placebo groups.

control might lead to substantial improvement of quality of life for both the patients and their caregivers.[10,15]

Although a decrement in language function is evident and important in patients with moderate-to-severe AD, it is often difficult to evaluate changes in these symptoms. One of the reasons is that the assessment tools that are available are limited. To overcome this limitation, SIB-L was developed as a reliable measurement to evaluate the effects of treatment on language function.[10] SIB-L comprises the largest proportion of SIB, which is a scale to evaluate cognitive function in patients with moderate-to-severe AD who may have floor effect.[20] Using the SIB-L score, the benefits of donepezil 23 mg/day versus donepezil 10 mg/day for language function was demonstrated in patients with moderate-to-severe AD.[11] Like the GV1001 1.12 mg group in our study, the donepezil 23 mg/day treatment group showed an improvement in language function above baseline. The beneficial effect of memantine compared to placebo, on language function in patients with moderate-to-severe AD, was also reported using the SIB-L score.[12] However, no improvement was found in the SIB-L score. The effect of galantamine treatment in patients with severe AD was analyzed using SIB, but failed to show a beneficial effect on language functions.[21] Rivastigmine was evaluated

https://doi.org/10.12779/dnd.2023.22.3.100

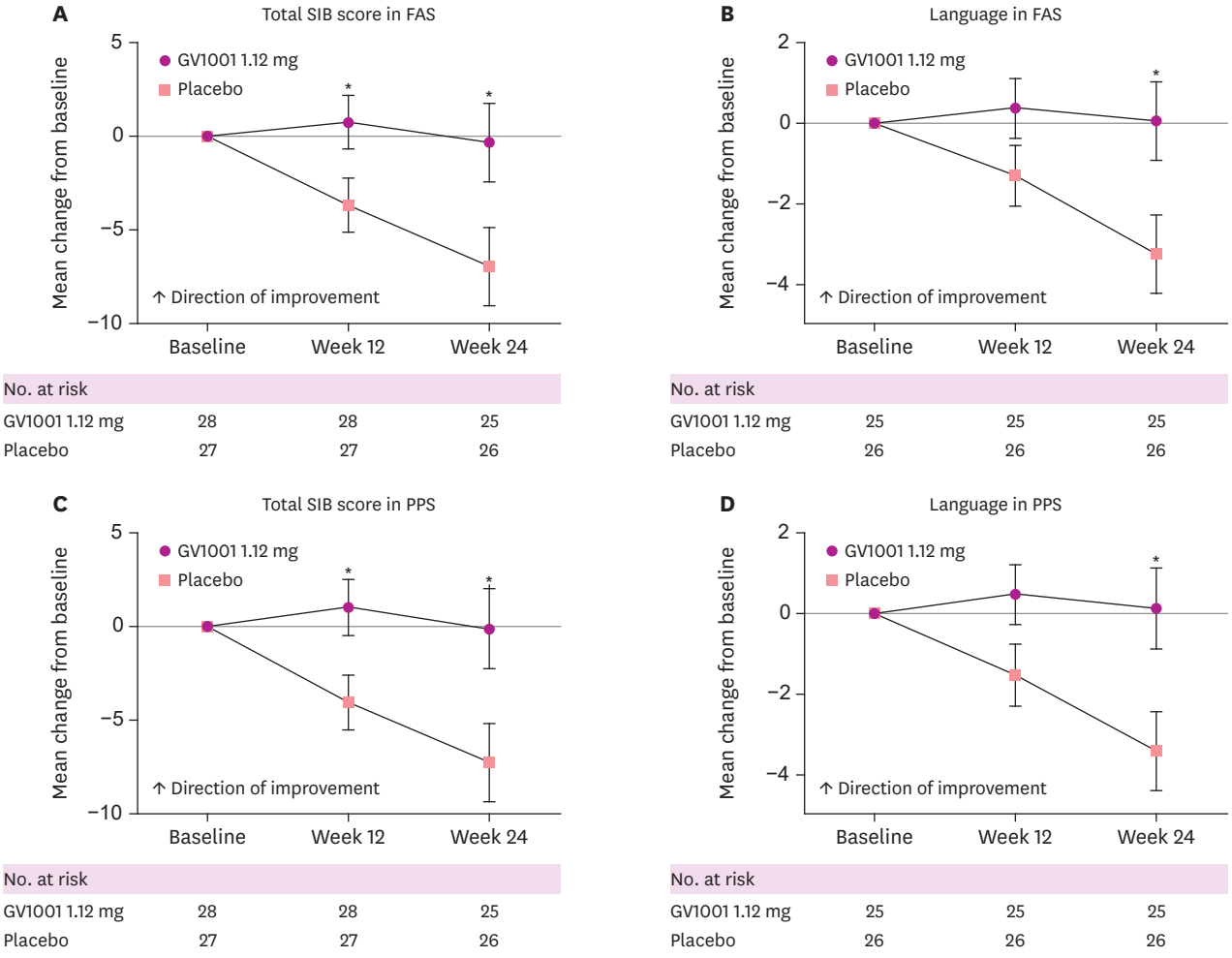

Fig. 2. Effects of GV1001 on the total SIB and SIB-L scores.
In both FAS (A) and PPS (C), the patients assigned to the 1.12 mg GV1001 group demonstrated a significantly better mean change in the total SIB scores from baseline at weeks 12 and 24, compared to the placebo group. Among the subscales, the SIB–L scale showed a significant benefit in the GV1001 group compared to the placebo group at week 24 (B and D). Error bars indicate the standard error.
SIB: Severe Impairment Battery, SIB-L: Severe Impairment Battery-Language, FAS: full analysis set, PPS: per-protocol set.
*p<0.05 (GV1001 vs. placebo).

among patients with mild-to-moderate AD using the Alzheimer's Disease Assessment Scale-Cognitive subscale, but the benefits for language function are conflicting.[22,23]

The reasons for GV1001 showing a better effect on language function than placebo were not investigated in the current study. It is possible that the diverse neuroprotective effects of GV1001, such as anti-apoptotic, anti-inflammatory, anti-aging, antioxidant, and mitochondrial-stabilizing effects, which have been previously reported,[6,7] may have influenced these results. Additional *in vitro* and *in vivo* studies are required to further investigate the underlying mechanisms of GV1001.

This study had several limitations. First, the enrolled patients were of a single ethnicity, and the number of patients was relatively small. However, showing the benefits of GV1001 in language function in this population is meaningful, and warrants a clinical trial with a multiethnic and larger number of patients. Second, the results of the current study may have been underpowered to detect the significant efficacy of GV1001 in some subgroups.

https://doi.org/10.12779/dnd.2023.22.3.100

In conclusion, this analysis suggests that GV1001 1.12 mg is safe, and may be beneficial for language function in patients with moderate-to-severe AD as measured by the SIB-L scale. These findings indicate that GV1001 may support communication in patients with advanced AD whose language function is critical to improving their quality of life.

AVAILABILITY OF DATA AND MATERIAL

Access to participant-level data from this study will not be made available, while GV1001 is in clinical trials for Alzheimer's disease and waiting for approval from the US Food and Drug Administration. Thereafter, all data supporting this study will be shared by qualified academic researchers after obtaining the consent of researchers.

REFERENCES

1. Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. Front Aging Neurosci 2022;14:937486.
PUBMED | CROSSREF
2. Koh SH, Kwon HS, Choi SH, Jeong JH, Na HR, Lee CN, et al. Efficacy and safety of GV1001 in patients with moderate-to-severe Alzheimer's disease already receiving donepezil: a phase 2 randomized, double-blind, placebo-controlled, multicenter clinical trial. Alzheimers Res Ther 2021;13:66.
PUBMED | CROSSREF
3. Farlow MR, Miller ML, Pejovic V. Treatment options in Alzheimer's disease: maximizing benefit, managing expectations. Dement Geriatr Cogn Disord 2008;25:408-422.
PUBMED | CROSSREF
4. Ghezzi L, Scarpini E, Galimberti D. Disease-modifying drugs in Alzheimer's disease. Drug Des Devel Ther 2013;7:1471-1478.
PUBMED | CROSSREF
5. Cummings J. Anti-amyloid monoclonal antibodies are transformative treatments that redefine Alzheimer's disease therapeutics. Drugs 2023;83:569-576.
PUBMED | CROSSREF
6. Park HH, Lee KY, Park DW, Choi NY, Lee YJ, Son JW, et al. Tracking and protection of transplanted stem cells using a ferrocenecarboxylic acid-conjugated peptide that mimics hTERT. Biomaterials 2018;155:80-91.
PUBMED | CROSSREF
7. Park HH, Yu HJ, Kim S, Kim G, Choi NY, Lee EH, et al. Neural stem cells injured by oxidative stress can be rejuvenated by GV1001, a novel peptide, through scavenging free radicals and enhancing survival signals. Neurotoxicology 2016;55:131-141.
PUBMED | CROSSREF
8. Saxton J, McGonigle-Gibson KL, Swihart AA, Miller VJ, Boller F. Assessment of the severely impaired patient: description and validation of a new neuropsychological test battery. Psychol Assess 1990;2:298-303.
CROSSREF
9. Schmitt FA, Ashford W, Ernesto C, Saxton J, Schneider LS, Clark CM, et al. The severe impairment battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11 Suppl 2:S51-S56.
PUBMED | CROSSREF
10. Ferris S, Ihl R, Robert P, Winblad B, Gatz G, Tennigkeit F, et al. Severe Impairment Battery Language scale: a language-assessment tool for Alzheimer's disease patients. Alzheimers Dement 2009;5:375-379.
PUBMED | CROSSREF
11. Ferris SH, Schmitt FA, Saxton J, Richardson S, Mackell J, Sun Y, et al. Analyzing the impact of 23 mg/day donepezil on language dysfunction in moderate to severe Alzheimer's disease. Alzheimers Res Ther 2011;3:22.
PUBMED | CROSSREF
12. Ferris S, Ihl R, Robert P, Winblad B, Gatz G, Tennigkeit F, et al. Treatment effects of Memantine on language in moderate to severe Alzheimer's disease patients. Alzheimers Dement 2009;5:369-374.
PUBMED | CROSSREF

13. Ferris S, Karantzoulis S, Somogyi M, Meng X. Rivastigmine in moderately severe-to-severe Alzheimer's disease: Severe Impairment Battery factor analysis. Alzheimers Res Ther 2013;5:63.
PUBMED | CROSSREF
14. Mecocci P, Bladström A, Stender K. Effects of memantine on cognition in patients with moderate to severe Alzheimer's disease: *post-hoc* analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies. Int J Geriatr Psychiatry 2009;24:532-538.
PUBMED | CROSSREF
15. Savundranayagam MY, Hummert ML, Montgomery RJ. Investigating the effects of communication problems on caregiver burden. J Gerontol B Psychol Sci Soc Sci 2005;60:S48-S55.
PUBMED | CROSSREF
16. Hendryx-Bedalov PM. Alzheimer's dementia. Coping with communication decline. J Gerontol Nurs 2000;26:20-24.
PUBMED | CROSSREF
17. Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia 2004;42:1212-1222.
PUBMED | CROSSREF
18. Ferrell BA. Pain evaluation and management in the nursing home. Ann Intern Med 1995;123:681-687.
PUBMED | CROSSREF
19. Tsai PF, Chang JY. Assessment of pain in elders with dementia. Medsurg Nurs 2004;13:364-369, 390.
PUBMED
20. Schmitt FA, Cragar D, Ashford JW, Reisberg B, Ferris S, Möbius HJ, et al. Measuring cognition in advanced Alzheimer's disease for clinical trials. J Neural Transm Suppl 2002;62:135-148.
PUBMED | CROSSREF
21. Burns A, Bernabei R, Bullock R, Cruz Jentoft AJ, Frölich L, Hock C, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. Lancet Neurol 2009;8:39-47.
PUBMED | CROSSREF
22. Grossberg GT, Schmitt FA, Meng X, Tekin S, Olin J. Reviews: effects of transdermal rivastigmine on ADAS-cog items in mild-to-moderate Alzheimer's disease. Am J Alzheimers Dis Other Demen 2010;25:627-633.
PUBMED | CROSSREF
23. Klimova B, Maresova P, Valis M, Hort J, Kuca K. Alzheimer's disease and language impairments: social intervention and medical treatment. Clin Interv Aging 2015;10:1401-1407.
PUBMED | CROSSREF