Protocol

진행성 핵상 마비 환자를 대상으로 GV1001 0.56 또는 1.12 mg/day 피하 투여 시 질환의 중증도 개선 효과와 안전성을 탐색하기 위한 다기관, 무작위배정, 이중 눈가림, 위약 대조, 평행 설계, 전향적, 제2a상 임상시험

A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel design, Prospective, Phase IIa Exploratory Clinical Trial to evaluate the efficacy and safety of Subcutaneous Administration of GV1001 0.56 or 1.12 mg/day in Patients with Progressive Supranuclear Palsy

Protocol No.	GV1001-PSP-CL2-011
Version No.	5.1
Version Date	15 Mar 2024
Investigational Product	GV1001
Target Disease	Progressive supranuclear palsy
Clinical Study Phase	Phase 2a
Clinical Study Sponsor	GemVax&KAEL Co., Ltd. [redacted]
Coordinating Investigator	Professor [redacted], Department of Neurology, SMG-SNU Boramae Medical Center

CONFIDENTIALITY STATEMENT

All information contained in this protocol is provided for the principal investigator and sub-investigators, the Institutional Review Board (IRB), and health authorities, and may not be disclosed to third parties without a prior written consent of the sponsor and the principal investigator.

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[Protocol Establishment/Revision History]

Document history including this protocol:

Version	Date	Summary of Changes
1.0	18 Oct 2022	Initial protocol
1.1	30 Nov 2022	• Change of manufacturer of study drug • Clarification of phrases on the collection of human-derived samples • Clarification of phrases in order to conduct the final visit schedule of dropped out subjects according to Visit 16 • Clarification of the labeling of the study drug and comparator (placebo) • New establishment of section [13.9.2 Investigator's obligations]
2.0	15 Feb 2023	[Revision according to the supplementary request from the Ministry of Food and Drug Safety] • Clarification of Clinical study duration • Exclusion Criteria 6): Change of the criteria related to tumor history prior to participation in the clinical study • Exclusion Criteria 10): Clarification of wording of the contraceptive period and addition of the detailed criteria for menopause • Added number of laboratory tests and pregnancy tests [Other changes] • After deleting the contents of study sites and principal investigators, etc. in the protocol, add a phrase as "See Appendix" and change the relevant Appendix 1 • Change of shelf life of study drug
2.1	18 May 2023	• Extension of screening period: 2 weeks → 4 weeks • Changes related to collecting human-derived samples - Change the number of cerebrospinal fluid collections: 3 times → 2 times (collection at Visit 10 deleted) - Change from Visit 2 → Visit 1 - Setting Visit 1 to allow separate visits for collecting human-derived samples
3.0	03 Aug 2023	• Inclusion criteria 7): Change in guardian accompanying conditions • Clarification of information and labeling of investigational product • Dropout Criteria: Deletion of dropout criteria in case of major protocol violations • Change in term of adverse events • Revision of Appendix 1 due to changes in study sites, principal investigator, and sample analysis institution, etc.
4.0	22 Nov 2023	• Inclusion criteria 7): Addition of a condition allowing companions other than the guardian when visiting study sites except for efficacy evaluation visits • Added appearance descriptions of investigational drugs • Addition of types of syphilis test • Revision of Appendix 1 due to changes in the principal investigator, etc.
5.0	08 Dec 2023	• Inclusion criteria 7): Deletion of the exceptional condition for accompanying guardian

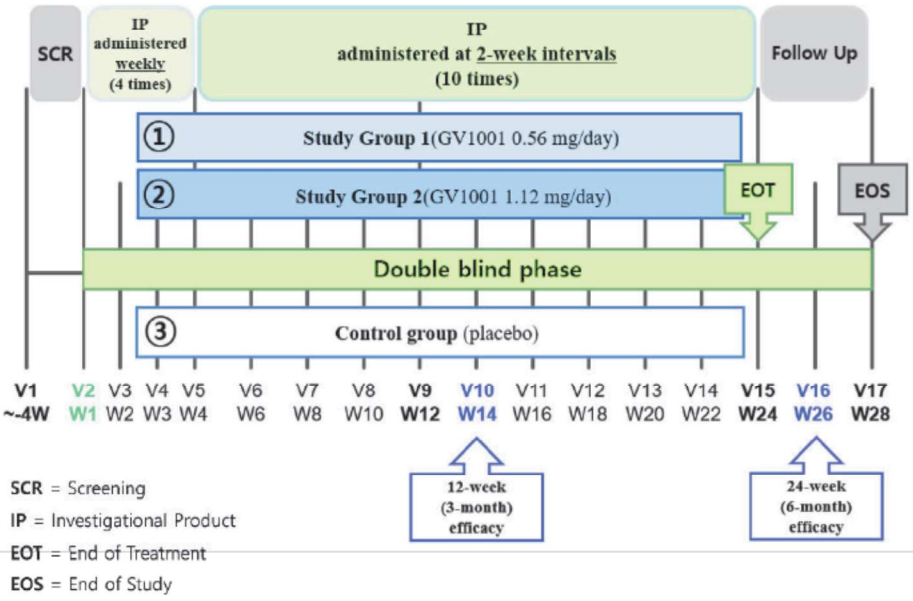
5.1	15 Mar 2024	• 6.4. Blinding and Unblinding: Clarification of wording for person in charge of dilution and administration • Addition of phrases regarding secondary use of human-derived samples, etc.

[Protocol Synopsis]

Clinical Study Sponsor	GemVax&KAEL Co., Ltd. [redacted]		
Item Name (Code Name)	GV1001	**Main Ingredient**	Tertomotide HCl
Clinical Study Title	진행성 핵상 마비 환자를 대상으로 GV1001 0.56 또는 1.12 mg/day 피하 투여 시 질환의 중증도 개선 효과와 안전성을 탐색하기 위한 다기관, 무작위배정, 이중 눈가림, 위약 대조, 평행 설계, 전향적, 제2a상 임상시험 A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel design, Prospective, Phase IIa Exploratory Clinical Trial to evaluate the efficacy and safety of Subcutaneous Administration of GV1001 0.56 or 1.12 mg/day in Patients with Progressive Supranuclear Palsy		
Clinical Study Identification No.	GV1001-PSP-CL2-011		
Coordinating Investigator	Professor [redacted], Department of Neurology, SMG-SNU Boramae Medical Center		
Study Sites and Principal Investigators	See [Appendix 1]. List of clinical trial participants and clinical trial pharmacists		
Clinical Study Duration	Approximately 24 months from the date of approval by the Ministry of Food and Drug Safety and the IRBs of study sites		
Target Disease	Progressive supranuclear palsy (PSP)		
Clinical Study Objectives	**[Primary Objective]** To explore the efficacy and evaluate the safety of GV1001 0.56 mg/day or 1.12 mg/day administered for 24 weeks on the severity of disease in patients with progressive supranuclear palsy. **[Secondary Objectives]** To collect source data to determine the possibility of progression to the next stage of development and to subsequent clinical studies by analyzing the clinical and biological parameters associated with the treatment response and safety information of 2 dose levels of GV1001, 0.56 mg/day or 1.12 mg/day, in patients with progressive supranuclear palsy.		
Clinical Study Phase and Design	Multicenter, randomized, double-blind, placebo-controlled, parallel design, prospective, Phase 2a exploratory clinical study		
Target Number of Subjects	This is a Phase 2a exploratory clinical study conducted for the purposes of collecting initial safety and efficacy information on the investigational product GV1001 in patients with progressive supranuclear palsy as well as providing the basis for design, evaluation items, and evaluation methods for subsequent clinical studies. This is an exploratory study to estimate the clinically significant effect size to demonstrate the efficacy of this investigational product in patients with progressive supranuclear palsy. Accordingly, the number of subjects was not calculated based on statistical considerations, and it is intended to set 20 subjects per group since the minimum number of subjects required in a pilot study is 12 subjects[21] and approximately 30 subjects can be considered according to the rule of thumb[22), 23]. Furthermore, considering a dropout rate of 20%, a total of 75 subjects with 25 subjects per group will be enrolled.		

Investigational Product	• Study drug: - Study drug 1: GV1001 0.84 mg/vial - Study drug 2: GV1001 1.68 mg/vial • Comparator: - Placebo of GV1001
Method and Duration of Investigational Product Administration	The study drug or the placebo will be administered once weekly for the first 4 weeks (1 month), and then administered 10 times at 2-week intervals for 20 weeks (5 months) for a total of 14 subcutaneous doses over 24 weeks (6 months).
Inclusion Criteria	1) Patients aged ≥41 years to ≤85 years 2) Patients clinically diagnosed with a probable PSP (Richardson type [PSP-RS] or parkinsonian type [PSP-p]) by the diagnostic criteria for PSP developed by the International Parkinson and Movement Disorders Society Task Force 3) In the case of the PSP-RS type, patients with clearly identified supranuclear ophthalmoplegia (SOP) according to the judgment of the investigator (e.g., the sum of scores in the ocular motor part of the PSP-rating scale must be ≥5 points or the downgaze [voluntary downward command movement] score must be ≥2 points). In the case of the PSP-p type, patients identified as having shown little or no response to previous administration of levodopa according to the judgment of the investigator during the course of treatment 4) Patients who had been taking a stable dose of a neurological drug for at least 1 month prior to screening without changes in the dose 5) Patients who are able to walk 3 meters or more independently or with assistive devices 6) Patients with at least 15 points on the Korean Mini-Mental State Examination (K-MMSE) at the screening visit (However, the results of a test performed at the study site within 2 weeks prior to the screening visit may be used if available.) 7) Patients who have a guardian who can accompany the patient at all visits according to the schedule of this clinical study, and who is able to supervise the subject's compliance with the test and examination procedures performed at the visits and provide information on the subject's indication, and whose guardians have provided a written consent for participation in the clinical study 8) Patients and/or their representatives who have voluntarily provided a written consent for participation in this clinical study
Exclusion Criteria	1) Patients who fall under any of the following based on the CT/MRI scan results and neurological examinations performed within 12 months of screening or at screening - Presence of structural lesions (vascular, neoplastic, inflammatory, infectious, demyelinating, etc.) that can clinically affect the patient's symptoms of progressive supranuclear palsy on brain CT or MRI - Suspected concurrent onset of central nervous system diseases* other than progressive supranuclear palsy that, according to clinical judgment, can cause parkinsonism *Dementia or motor disorders due to vascular brain disease, subdural hematoma, normal pressure hydrocephalus, brain tumor, Alzheimer's disease, multiple system atrophy, Creutzfeldt-Jakob disease, etc. 2) Patients with a history of known or suspected seizures (including febrile seizure) 3) Patients with a recent unexplained loss of consciousness within 3 months prior to screening or a history of significant head trauma with loss of consciousness 4) Patients with acute or unstable cardiovascular disease, uncontrolled hypertension (exceeding 160/100 mmHg), uncontrolled diabetes (insulin-dependent or HbA1c

	>8%), or any other medical condition that can interfere with completing the clinical study 5) Patients with hypersensitivity reactions to the ingredients of the investigational product 6) Patients with a history of cancer within 5 years prior to screening (however, nonmetastatic basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or nonprogressive prostate cancer are allowed) 7) Patients with abnormal renal function (creatinine clearance [CLcr] < 30 mL/min on screening test) 8) Patients with severe liver function abnormalities (ALT or AST is ≥2.5 times the upper limit of normal on screening test) 9) Patients weighing ≤35 kg 10) The woman of childbearing potential and male subjects who do not agree to contraception using medically acceptable methods (surgical sterilization, intrauterine contraceptive device, tubal ligation, double-barrier methods [combined use of barrier methods such as male condoms, female condoms, cervical caps, contraceptive diaphragms, and contraceptive sponges]), a single-barrier method with spermicide, and complete abstinence) during the clinical study and up to 90 days after the end (discontinuation) of their participation in the clinical study. However, women who have gone through menopause* or women or men who have undergone surgical sterilization (vasectomy, bilateral tubal ligation, etc.) before participating in the clinical study can participate even if they do not agree to contraception. * In this clinical study, menopause is defined as one or more of the following. (1) Female subjects aged ≥55 years who have had amenorrhea for more than 1 year (2) Female subjects aged ≥41 years to <55 years who have had amenorrhea for more than 1 year and have a serum follicle stimulating hormone (FSH) level ≥ 30 mIU/mL (3) In case of artificial menopause caused by bilateral oophorectomy 11) Pregnant or breastfeeding women 12) Patients who participated in another clinical study within 4 weeks prior to screening and were administered investigational products or were applied investigational medical devices 13) Patients who were administered the study drug (GV1001) of this clinical study within 12 months prior to screening 14) Patients who participated in a clinical study for progressive supranuclear palsy within 6 months prior to screening 15) Other patients judged by the investigator as ineligible to participate in this clinical study
Clinical Study Methodology	This is a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel design, prospective, Phase 2a exploratory clinical study. If the subject and/or the subject's representative provide a written consent to participate in this clinical study, the required examinations and tests will be performed at the screening visit, and the screening period will run for 4 weeks or shorter. Subjects who are ultimately determined as eligible by the inclusion/exclusion criteria after screening will be randomized at a 1:1:1 ratio to Study Group 1 (GV1001 0.56 mg/day), Study Group 2 (GV1001 1.12 mg/day), or the placebo group depending on the study site in which they are enrolled. Depending on the randomization results, subjects will be administered the investigational product (study drug or placebo) once weekly for the first 4 weeks (1 month), and then administered 10 times at 2-week intervals for 20 weeks (5 months) for a total of 14 doses over 24 weeks (6 months).

	All subjects will visit the study site according to the planned clinical study schedule to receive the investigational product and to be evaluated for efficacy and safety. To ensure the objectivity and accuracy of the study results, the efficacy evaluators evaluating the PSP-rating scale will be limited to neurologists who have been sufficiently educated and trained, and the collection of efficacy and safety evaluation data and biomarkers will be performed in a consistent order at each visit. ※ Neurological drugs administered at a stable dose for at least 1 month prior to a subject's participation in this clinical study (prior to screening) will be continued without changing the dose during the clinical study participation period. 
Endpoints and Evaluation Method	**[Primary Efficacy Endpoint]** Change from the baseline in the total score of PSP-rating scale after 24 weeks (6 months) of investigational product administration **[Secondary Efficacy Endpoints]** 1) Change from the baseline in the total score of PSP-rating scale after 12 weeks (3 months) of investigational product administration 2) Change from the baseline in the Montreal Cognitive Assessment - Korea (MoCA-K) after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration 3) Change from the baseline in the Korean Frontal Assessment Battery (K-FAB) after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration 4) Change from the baseline in the England & Schwab Activity of Daily Living (ES ADL) scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration 5) Change from the baseline in the score of each domain of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration 6) Change from the baseline in the score of each item of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration

	[Exploratory Endpoints] 1) Change from the baseline in total tau (t-tau), phosphorylated tau (p-tau), and neurofilament light chain (NfL) markers in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid after 24 weeks (6 months) of the investigational product administration 2) Change from the baseline in inflammatory cytokine markers (IL-6, IL-8, IL-2, IFN- γ, TNF-α, etc.) in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid after 24 weeks (6 months) of the investigational product administration 3) Change from the baseline in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid markers after 24 weeks (6 months) of investigational product administration, and correlation between clinical markers and treatment responses **[Safety Endpoints]** 1) Adverse events 2) Laboratory tests (hematology test, blood chemistry test, urinalysis) 3) Vital signs 4) Electrocardiogram

[Clinical Study Schedule]

Period	Screening	Double blind treatment phase														Follow Up	
Week	~-4	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 EOT	16	☎ 17 EOS
Visit window (days)	-	-	±3			±5										±5	±5
Subject Consent and Assignment of Screening Number	○																
Demographic Information	○																
Checking Medical/Surgical History	○	○															
Checking prior/concomitant medications	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Physical examination	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Vital signs	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Weight	○	○				○				○						○	
Height	○																
Electrocardiography[1]	○									○						○	
Laboratory tests[2]	○	○				○				○						○	
Urine hCG[3]	○	○				○		○		○		○		○		○	
Checking inclusion/exclusion criteria	○	○															
Randomization		○															
K-MMSE[4]	○																
PSP-rating scale	○									○						○	

Period		Screening	Double blind treatment phase														Follow Up	
Week		~-4	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 EOT	16	☎ 17 EOS
Visit window (days)		-	-	±3			±5										±5	±5
MoCA-K			○								○						○	
K-FAB			○								○						○	
ES ADL			○								○						○	
Brain CT[5]		(○)																
Collecting human-derived samples[6]	DNA, Plasma, Serum	○									○						○	
	Cerebrospinal fluid	○															○	
Investigational product administration[7]			○	○	○	○	○	○	○	○	○	○	○	○	○	○		
Adverse Event Assessment[8]			○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

[1] Electrocardiography: For the Visit 1 (screening) test, the results of a test performed within 3 months may be used if available, and retesting may be performed only once at the discretion of the investigator.

[2] Laboratory tests: For the Visit 1 (screening) tests, the results of tests performed within 4 weeks may be used if available, and retesting may be performed only once at the discretion of the investigator. At Visit 1 (screening), the serum FSH tests shall be performed to confirm menopause in women aged ≥41 years to <55 years who have experienced amenorrhea for more than 1 year.

- Hematology test: WBC, RBC, Hemoglobin, Hematocrit, Platelets count, WBC differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
- Blood chemistry test: BUN, Creatinine, Uric acid, Total bilirubin, Albumin, Total Protein, ALT, AST, γ-GTP, Alkaline phosphatase, Glucose, Total Cholesterol, HbA1c (performed only at screening visit)
- Serum Follicle Stimulating Hormone test: FSH (Performed only at screening visit for those who require confirmation of menopause)
- Urinalysis: Protein (Albumin), Glucose, Ketones, WBC, Blood (RBC)
- Blood coagulation test: INR (performed only at screening visit)
- Thyroid test: TSH, free T4 (performed only at screening visit)
- Syphilis, AIDS tests: VDRL or RPR, anti-HIV (performed only at screening visit)
- Serum creatinine clearance will be confirmed using the Cockcroft-Gault formula. (performed only at screening visit)

CLcr = [(140 − Age (years)] × Weight (kg) × 0.85 (for female subjects) / 72×Serum Creatinine (mg/dl)

[3] Urine hCG: Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal. However, for Visit 1 (screening), the subjects who performed the serum FSH test to confirm menopause when participating in the clinical study will also perform urine hCG pregnancy test.

[4] K-MMSE: The results of a test performed at the study site within 2 weeks prior to the screening visit may be used if available.

[5] Brain CT: This will be performed only on subjects without brain CT imaging within 12 months prior to the screening visit.

[6] Collecting human-derived samples: Human-derived samples (DNA, plasma, serum, and cerebrospinal fluid) will be collected for exploratory evaluations, and they will be transferred to the central lab for analysis and storage. However, in the case of cerebrospinal fluid, it will be collected only from subjects who have separately consented to collection of samples. For Visit 1 (screening), separate visits for collecting human-derived samples can be set up and implemented within the screening period.
[7] Investigational product administration: Subjects will be observed for approximately 20 minutes after the administration of the investigational product from Visit 2 to Visit 15.
[8] Adverse events assessment: Adverse events that occurred after the first administration of the investigational product will be identified, and prior to the first administration, it will be collected as medical history.

[Abbreviations and Terms]

Abbreviation	Full term
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CRO	Contract Research Organization
EOS	End of Study
EOT	End of Treatment
ES ADL	England & Schwab Activity Of Daily Living
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
hCG	human Chorionic Gonadotropin
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
K-FAB	Korean Frontal Assessment Battery
KGCP	Korean Good Clinical Practice
K-MMSE	Korean Mini-Mental State Examination
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
MoCA-K	Montreal Cognitive Assessment-Korean Version
NfL	Neurofilament-Light chain
PPS	Per-Protocol Set
PSP	Progressive Supranuclear Palsy
PSP-p	Progressive Supranuclear Palsy-parkinsonism
PSP-RS	Progressive Supranuclear Palsy-Richardson's Syndrome
PT	Preferred Term
p-Tau	phosphorylated Tau
RBC	Red Blood Cell
RPR	Rapid Plasma Reagin
SAE	Serious Adverse Event
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SOP	Supranuclear Ophthalmoplegia
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TNF	Tumor Necrosis Factor
TSH	Thyroid Stimulating Hormone
t-Tau	total Tau
VDRL	Venereal Disease Research Laboratory
WBC	White Blood Cell
γ-GTP	gamma-Glutamyl Transpeptidase

1. Clinical Study Title and Phase

1.1. Clinical Study Title

진행성 핵상 마비 환자를 대상으로 GV1001 0.56 또는 1.12 mg/day 피하 투여 시 질환의 중증도 개선 효과와 안전성을 탐색하기 위한 다기관, 무작위 배정, 이중 눈가림, 위약 대조, 평행 설계, 전향적, 제2a상 임상시험

A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel design, Prospective, Phase IIa Exploratory Clinical Trial to evaluate the efficacy and safety of Subcutaneous Administration of GV1001 0.56 or 1.12 mg/day in Patients with Progressive Supranuclear Palsy

1.2. Phase

Phase 2a clinical study

2. Study Sites, Principal Investigators, and Sponsor

See [Appendix 1]. List of clinical trial participants and clinical trial pharmacists

3. Introduction

3.1. Background and Rationale

3.1.1. Overview of Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a refractory neurodegenerative disease in which brain tissue shows 4-repeat (4R) tau protein aggregation and deposition, followed by progressive death of brain neurons, resulting in motor and cognitive impairment as well as emotional and behavioral regression. It shows rapid progression after the onset of symptoms and the patient dies within 5 to 8 years on average. As with most neurodegenerative diseases, it is difficult to confirm the exact prevalence or incidence of PSP because adequate population-based surveys have not been conducted. However, the prevalence is known to be 5 to 7 patients per 100,000 of the population[1)–3)] because of the rare occurrence of the disease worldwide. It has been reported that the proportion of patients diagnosed with PSP among patients who visit hospitals with an onset of Parkinsonism is approximately 5 to 6%.[4), 5)]

The pathologic mechanism of PSP is yet to be fully identified, but various mechanisms in the function and metabolism of tau protein in the brain nervous system are known to eventually result in aggregation of tau protein in cells and subsequent death of brain neurons that rapidly spreads into the brain nervous system, resulting in atrophy and degeneration of the brain.

The tau protein is a microtubule-associated protein (MAP) that stabilizes intracellular microtubules in the axon, a branch extending from the cell body of a neuron, and it mainly plays the role of regulating the assembly and migration of microtubules, spatial arrangement and composition, and transport through the axons of small organelles. The tau protein is finally synthesized as a protein after transcription and translation from a gene, and in this process, it undergoes modification processes such as phosphorylation, acetylation, and breaks to finally synthesize into a protein. In addition to PSP, neurodegenerative diseases characterized by the accumulation of tau protein such as Alzheimer's disease, corticobasal degeneration (CBD), Pick's disease, and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) are called tauopathies. The aforementioned protein synthesis process plays an important role in the pathophysiology that induces functional abnormalities of tau protein in tauopathies including PSP.

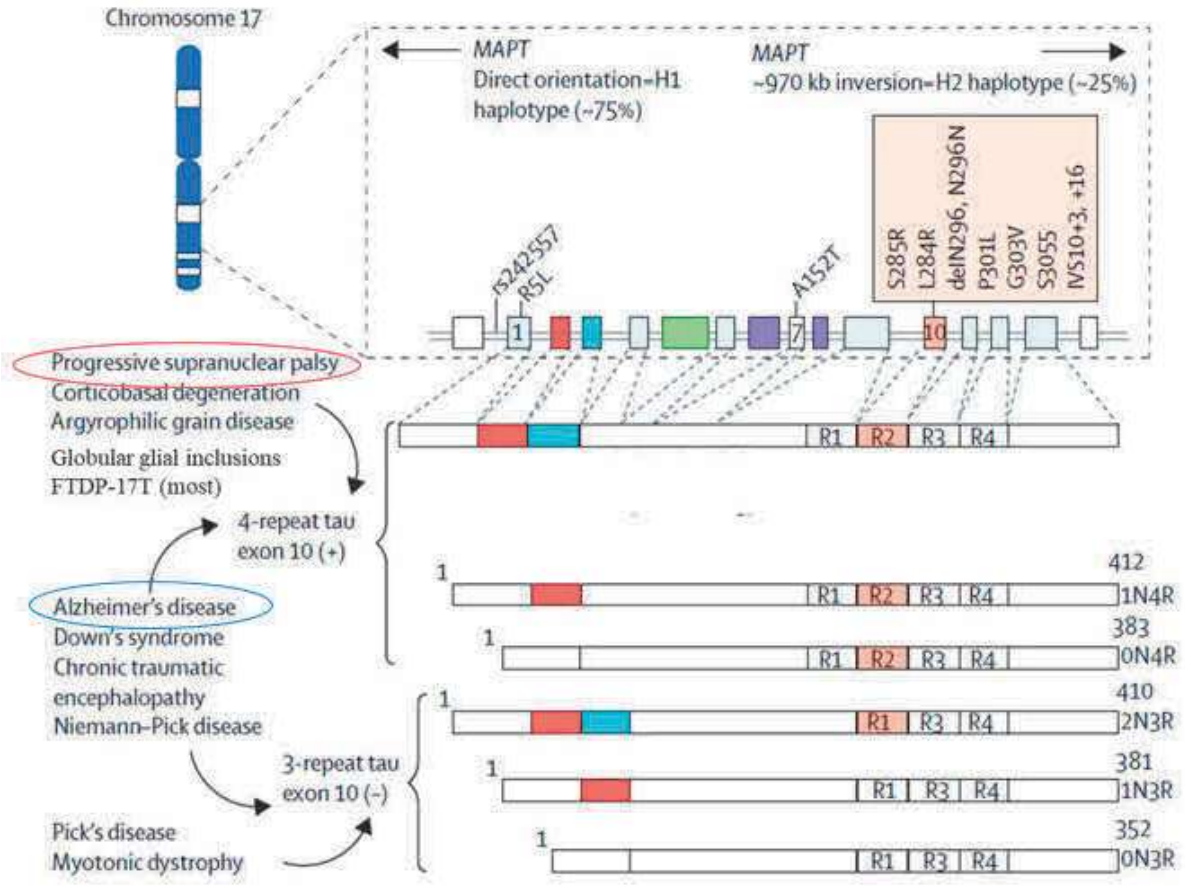


Figure 1 The MAPT locus, its pathological mutations, and tau protein isoforms

The tau protein is generated from the microtubule-associated protein tau (MAPT) gene (i.e., the tau gene) located at the q21 locus (17q21) of chromosome 17. The fact that mutations in the MAPT gene can cause FTDP-17 clearly supports the causal role of tauopathy in neurodegeneration.[6] The tau gene consists of a total of 16 exons numbered from 0 to 14.[7] Among them, according to the number of C-terminal (31 or 32 amino acids) amino acid repeats generated in exon 10 depending on the alternative splicing of exons 2, 3, and 10, it is classified as 3-repeat (3R) or 4-repeat (4R), respectively, if there are 3 or 4 repeated sequences. In addition, according to the number of insertion sequences of N-terminal (29 amino acids) present in exons 2 and 3, respectively, it is classified as 0N, 1N, or 2N if the number of insertion sequences is 0, 1, or 2. Summarizing the above, 6 tau isoforms are generated, ranging from 352 amino acids (shortest with 3R/0N) to 441 amino acids (longest with 4R/2N) in total. PSP is classified as a representative neurodegenerative disease of 4R tauopathy, and it can be seen that there are some common aspects with Alzheimer's disease in terms of pathophysiology[Figure 1].[8]

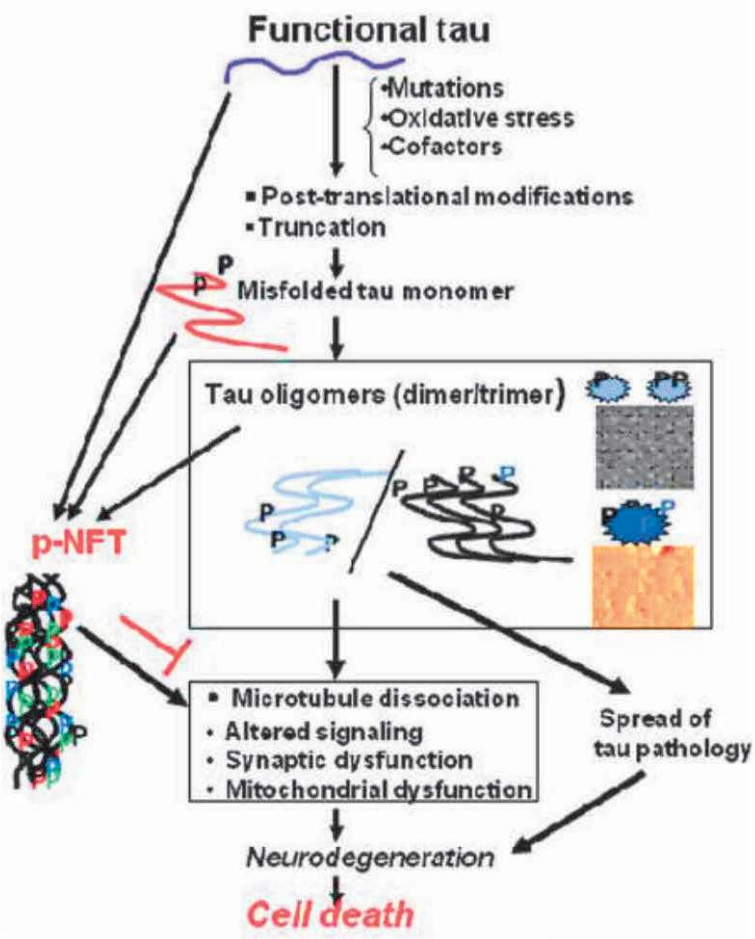


Figure 2 A schematic illustrating the central role of tau oligomers in neurodegeneration.

The tau monomers that are formed incorrectly during the modification process of protein synthesis are known to form tau oligomers, in which tau proteins are tangled and clumped together, and induce pathologies in brain neurons with the occurrence of hyperphosphorylation as well as cause apoptosis through various mechanisms, which ultimately results in neurodegenerative diseases.[Figure 2].[9)]

The latest strategy for the development of therapeutic agents based on the pathophysiology of tauopathies is as shown below[Table 1, Figure 3].[8)] The post-translational modification strategy is a strategy applied in common with therapeutic agents being developed to target Alzheimer's disease, and the drugs are being developed as oral or parenteral administration drugs, rather than antibodies (passive immunity) or active immunity or gene therapeutic agents.

Table 1 Treatment development strategy for tauopathies

Disease	Astrocytes		Oligodendrocytes		Neurons	Tau 3R-4R-Mutant
PSP	Tuft astr	(Pretangles/tangles)	Coiled	(Pretangles/tangles)	Pretangles/tangles	4R (a few prot astr 3R)
	Prot astr	(Pretangles/tangles)				
	Astr sppd	(Pretangles)				
CBD	Astr plaques	(Pretangles)	Coiled	(Pretangles/tangles)	Pretangles/tangles	4R
Elderly tauopathy	Astr sppd	(Pretangles)	–		Pretangles	4R
	TsA	(Pretangles/tangles)				
AGD	TsA	(Pretangles/tangles)	Coiled	(Pretangles/tangles)	Pretangles + AD*	4R
AD	TsA (when present)	(Pretangles/tangles)	–	–	Pretangles/tangles	4R/3R
PiD	React astr	(Pretangles)	Coiled	(Pretangles/tangles)	Pick bodies	3R (some fibrous astr 4R)
FTLD-tau/P301L	Astr prox gran incl	(Pretangles)	Coiled	(Pretangles/tangles)	Pretangles/tangles	4R mut
FTLD-tau/K317M	Astr tuft-li	(Tangles)	Coiled + globular	(Tangles)	Tangles	4R mut (a few glob incl 3R)
GGT	Tufted-like	(Tangles)	GGI	(Tangles)	Pretangles/rarely tangles	4R (a few GGIs 3R)

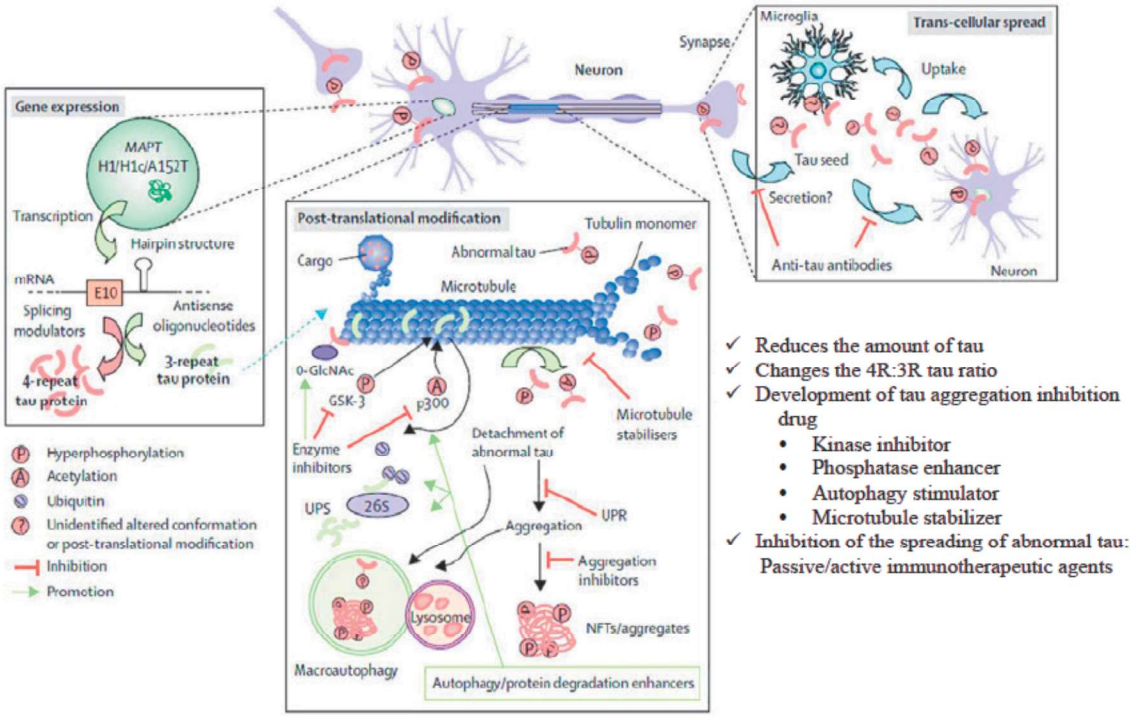


Figure 3 Potential therapeutic targets for progressive supranuclear palsy

3.1.2. Information on Existing Therapies

Currently, it is not an exaggeration to say that therapies for patients with progressive supranuclear palsy are nonexistent. Disease-specific drugs have not been developed to date, and several central nervous system drugs are being used as popular treatments for neurological disorders. Levodopa (L-dopa), a precursor of dopamine, is often used in patients with early progressive supranuclear palsy, but only about 40% of patients show limited response to L-dopa, and the effect of the drug on improving neurological symptoms is known to be minimal. In addition, amantadine can show some mild symptomatic improvement effects as it shows dopaminergic effects as well as concurrent anticholinergic and antiglutamatergic effects. However, many other central nervous system drugs have been administered to try to improve the symptoms of patients with progressive supranuclear palsy, but there are no drugs that can delay or improve neurological disorders to date. Besides this, botulinum toxin injections are used symptomatically to treat blepharospasm, which is a focal dystonia, as well as the accompanying apraxia of eyelid opening.

Based on the pathological mechanisms of PSP that have been emerging recently, the development of various drug treatments and immunotherapies is being attempted in developed countries overseas, and there are several drugs

that are undergoing preclinical and clinical study Phases 1 and 2.

3.1.3. Background of Clinical Study (Rationale)

The clinical study results of the above drugs under development are still not promising, and there are no drugs that were able to successfully move on to a Phase 3 clinical study. In addition to PSP, new-concept clinical studies on new drugs for refractory neurodegenerative diseases have recently been conducted in North America and Europe, and drugs that have been approved by the U.S. Food and Drug Administration (US FDA) for some rare and refractory diseases and have begun sales are not realistically accessible for domestic patients because of their astronomical costs. Furthermore, since the pharmaceutical companies that developed the drugs are often overseas R&D companies, they do not have global sales lines, and thus are not applicable to domestic patients. Even if a drug is not a treatment for rare refractory diseases, various investigational drugs for relatively common neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease take at least 5 to 10 years from the time of overseas sales in the US or Europe to their domestic introduction. Thus, waiting without appropriate treatment until the drugs developed overseas reach domestic sales is too dangerous for patients with neurodegenerative diseases whose first 3 years after diagnosis are crucial due the rapid progression of disease. Therefore, even in the case of PSP, which is a representative refractory neurodegenerative disease, the development of treatments that meet the treatment standards and circumstances of domestic patients is absolutely necessary in terms of the cost and efficiency of Korean healthcare.

Summarizing the above, PSP is a neurodegenerative disease caused by tau protein abnormalities, and the pathophysiology is similar to Alzheimer's disease in that it is a tauopathy. Therefore, based on experimental evidence showing that GV1001 will improve neuronal viability and reduce the amount of aggregated tau, and the results of a preceding Phase 2 clinical study (KG6/2016) on Alzheimer's disease that was conducted domestically, there is a need to develop it as a treatment for PSP as well. PSP, which is 3 times faster than relatively common neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease and is severely disabling, has no realistic treatment, and thus, the development of a treatment is desperately needed.

This clinical study has been planned in the form of a Phase 2 clinical study to scientifically verify the possibility of developing GV1001 as a treatment for PSP. Since GV1001 has already been studied in large-scale clinical studies on cancer diseases and Alzheimer's disease, and safety data have also been obtained from elderly patients with dementia, it is considered that the additional risks that occur in the process of developing it as a treatment for refractory neurodegenerative diseases such as PSP will be minimal. In addition, it is anticipated that it can become a breakthrough treatment if it is able to improve the symptoms that substantially lower the quality of life or partially reduce the speed of rapid progression that threatens life in PSP patients who have no existing treatments. Since the initial development process is conducted domestically, it has the conditions to be a very realistically useful drug that can be immediately applied to domestic patients if the clinical study is successful and product approval is obtained in the future. Therefore, there is an even more desperate need to conduct the clinical study domestically in Republic of Korea.

3.2. Mechanism of Action from Nonclinical Study Data of GV1001

- [redacted]
- No serious adverse events were reported for GV1001 in previously conducted nonclinical and clinical studies. In particular, safety in humans has been confirmed in various clinical studies on several target diseases in

which GV1001 was administered, with reports of only mild adverse events such as erythema at the site of administration and flu-like symptoms.

- Considering that GV1001 is a [redacted], *in vitro* and *in vivo* experiments were conducted under the assumption that the positive functions (i.e., cytoprotective effects, antioxidative effects, anti-inflammatory effects, etc.) [redacted] and these effects were confirmed as below. Therefore, it can be hypothesized that there will be therapeutic effects that can reduce apoptosis in neurodegenerative diseases such as Alzheimer's disease or PSP.

- First, the following were shown when experiments conducted in *in vitro* cell models and in transgenic animal models having *in vivo* Alzheimer etiologies[13] were examined.

1) [redacted]

Figure 4 [redacted]

2) [redacted]

Figure 5 [redacted]

3) [redacted]

Figure 6

4)

Figure 7

5)

Figure 8

6)

Figure 9

- In addition, the following were shown when the results of animal experiments conducted on a transgenic animal model ( ) with a tau etiology showing progressive supranuclear palsy disease were examined.

1)

Figure 10

2)

Figure 11

3)

Figure 12

4)

[redacted]

1) [redacted]

2) [redacted]

[redacted]

3) [redacted]

[redacted]

4) [redacted]

Figure 13

4)

1)

2)

Figure 14

Summarizing these experiment results, it can be inferred that GV1001, through various mechanisms, is able to effectively inhibit apoptosis caused by the main pathological mechanism of neuronal degeneration. Furthermore, it can be summarized that the drug will show efficacy in PSP because the potential mechanisms reduce reactive oxygen species, prevent apoptosis, inhibit formation of total tau and tau oligomers, decrease the amount of aggregated tau protein, and promote spontaneous neurogenesis.

3.3. Results of Past Clinical Studies

To date, GV1001 has been applied to patients with a variety of diseases through clinical studies and individual therapeutic use approval procedures. For PSP, the target disease of this clinical study, GV1001 was administered for .

The PSP-rating scale (PSP-RS)[14] is a measure of efficacy validated as a method of quantitatively evaluating the neurological status of patients with PSP.

[redacted]

Figure 15 [redacted]

[redacted]

For reference, in a large-scale Phase 2/3 Davunetide clinical study[16], the progression of disease in PSP patients who participated increased by 6.8 points on average after 6 months of treatment contrary to expectations, and thus, it was shown that the natural progression of worsening symptoms could not be changed.

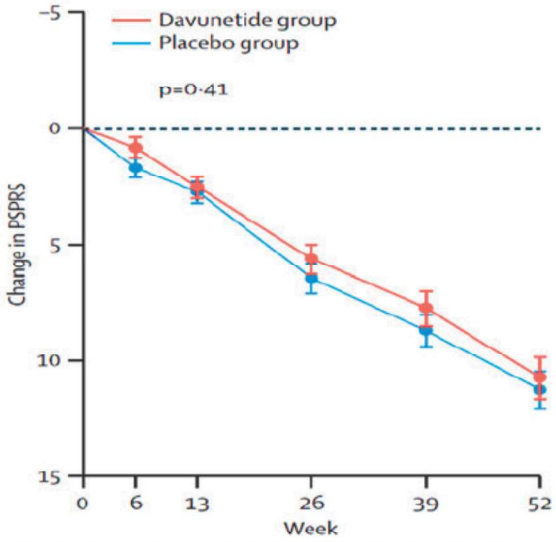


Figure 16 PSP-RS change in PSP patients administered Davunetide or placebo in clinical trial of NCT01110720

3.4. Rationale for Dose Setting

The dose of the investigational product to be used in this clinical study was determined by the process of deriving the maximum recommended starting dose for human clinical studies on new drugs.

[redacted]

[redacted]

Summarizing the above results, the safe starting dose for the PSP clinical study was 0.56 mg/day ([redacted]), and the second dose was determined as 1.12 mg/day ([redacted]).

In addition, at the previously implemented doses of GV1001 0.56 to 1.12 mg/day used in patients approved for therapeutic use of the drug, no significant adverse events were reported, similar to other clinical studies, and significant clinical improvements were shown in the change of the PSP-RS score. Moreover, since results of improvement could be observed in other clinical symptoms, it was determined that the dose of 0.56 to 1.12 mg/day is appropriate in this clinical study.

Based on the above considerations, this clinical study intends to conduct a final validation on the efficacy and safety of two doses of GV1001 0.56 mg/day and 1.12 mg/day.

4. Study Objectives

4.1. Primary Objective

To explore the efficacy and evaluate the safety of GV1001 0.56 mg/day or 1.12 mg/day administered for 24 weeks on the severity of disease in patients with progressive supranuclear palsy.

4.2. Secondary Objectives

To collect source data to determine the possibility of progression to the next stage of development and to subsequent clinical studies by analyzing the clinical and biological parameters associated with the treatment response and safety information of 2 dose levels of GV1001, 0.56 mg/day or 1.12 mg/day, in patients with progressive supranuclear palsy.

5. Clinical Study Population

5.1. Target Number of Subjects

Total number of subjects: 75 subjects (75 subjects in total with 25 subjects per group considering a dropout rate of 20%)

	Study Group 1	Study Group 2	Control Group	Total Number of Subjects
Number of Subjects	20	20	20	60
Number of Subjects Considering Dropout (20%)	25	25	25	75

5.2. Target Patients

Progressive supranuclear palsy

5.3. Inclusion Criteria

1) Patients aged ≥ 41 years to ≤ 85 years
2) Patients clinically diagnosed with a probable PSP (Richardson type [PSP-RS] or parkinsonian type [PSP-p]) by the diagnostic criteria for PSP developed by the International Parkinson and Movement Disorders Society Task Force
3) In the case of the PSP-RS type, patients with clearly identified supranuclear ophthalmoplegia (SOP) according to the judgment of the investigator (e.g., the sum of scores in the ocular motor part of the PSP-rating scale must be ≥ 5 points or the downgaze [voluntary downward command movement] score must be ≥ 2 points). In the case of the PSP-p type, patients identified as having shown little or no response to previous administration of levodopa according to the judgment of the investigator during the course of treatment
4) Patients who had been taking a stable dose of a neurological drug for at least 1 month prior to screening without changes in the dose
5) Patients who are able to walk 3 meters or more independently or with assistive devices
6) Patients with at least 15 points on the Korean Mini-Mental State Examination (K-MMSE) at the screening visit (however, the results of a test performed at the study site within 2 weeks prior to the screening visit may be used if available)
7) Patients who have a guardian who can accompany the patient at all visits according to the schedule of this clinical study, and who is able to supervise the subject's compliance with the test and examination procedures performed at the visits and provide information on the subject's indication, and whose guardians have provided a written consent for participation in the clinical study
8) Patients and/or their representatives who have voluntarily provided a written consent for participation in this clinical study

5.4. Exclusion Criteria

1) Patients who fall under any of the following based on the CT/MRI scan results and neurological examinations performed within 12 months of screening or at screening
   - Presence of structural lesions (vascular, neoplastic, inflammatory, infectious, demyelinating, etc.) that can clinically affect the patient's symptoms of progressive supranuclear palsy on brain CT or MRI
   - Suspected concurrent onset of central nervous system diseases* other than progressive supranuclear palsy that, according to clinical judgment, can cause parkinsonism
     *Dementia or motor disorders due to vascular brain disease, subdural hematoma, normal pressure hydrocephalus, brain tumor, Alzheimer's disease, multiple system atrophy, Creutzfeldt-Jakob disease, etc.
2) Patients with a history of known or suspected seizures (including febrile seizure)
3) Patients with a recent unexplained loss of consciousness within 3 months prior to screening or a history of significant head trauma with loss of consciousness

4) Patients with acute or unstable cardiovascular disease, uncontrolled hypertension (exceeding 160/100 mmHg), uncontrolled diabetes (insulin-dependent or HbA1c >8%), or any other medical condition that can interfere with completing the clinical study
5) Patients with hypersensitivity reactions to the ingredients of the investigational product
6) Patients with a history of cancer within 5 years prior to screening (however, nonmetastatic basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or nonprogressive prostate cancer are allowed)
7) Patients with abnormal renal function (creatinine clearance [CLcr] < 30 mL/min on screening test)
8) Patients with severe liver function abnormalities (ALT or AST is ≥ 2.5 times the upper limit of normal on screening test)
9) Patients weighing ≤ 35 kg
10) The woman of childbearing potential and male subjects who do not agree to contraception using medically acceptable methods (surgical sterilization, intrauterine contraceptive device, tubal ligation, double-barrier methods [combined use of barrier methods such as male condoms, female condoms, cervical caps, contraceptive diaphragms, and contraceptive sponges]), a single-barrier method with spermicide, and complete abstinence) during the clinical study and up to 90 days after the end (discontinuation) of their participation in the clinical study.
However, women who have gone through menopause* or women or men who have undergone surgical sterilization (vasectomy, bilateral tubal ligation, etc.) before participating in the clinical study can participate even if they do not agree to contraception.
* In this clinical study, menopause is defined as one or more of the following
(1) Female subjects aged ≥55 years who have had amenorrhea for more than 1 year
(2) Female subjects aged ≥41 years to <55 years who have had amenorrhea for more than 1 year and have a serum follicle stimulating hormone (FSH) level ≥ 30 mIU/mL
(3) In case of artificial menopause caused by bilateral oophorectomy
11) Pregnant or breastfeeding women
12) Patients who participated in another clinical study within 4 weeks prior to screening and were administered investigational products or were applied investigational medical devices
13) Patients who were administered the study drug (GV1001) of this clinical study within 12 months prior to screening
14) Patients who participated in a clinical study for progressive supranuclear palsy within 6 months prior to screening
15) Other patients judged by the investigator as ineligible to participate in this clinical study

5.5. Dropping Out

5.5.1. Definition

Subjects who have been randomized but are unable to participate for the entire duration of the clinical study for any reason will be classified as dropouts. Subjects may discontinue the study at any time at their own request, or may be dropped out at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons.
The investigator shall ask the subject regarding the reason for dropping out, and request the subject to visit the study site for the last time to undergo the tests performed at Visit 16. If applicable, every effort shall be made to follow up on the subject with regard to unresolved adverse events.

5.5.2. Dropout Criteria

The following are the cases in which the subjects may request to discontinue the clinical study, or in which they may be discontinued or dropped out according to a discussion between the investigator and the sponsor.

① The subject or the subject's representative has withdrawn consent to participate in the clinical study.

② Violation of the inclusion/exclusion criteria is found during the clinical study.
③ Continuation of the clinical study is difficult because of adverse events or serious adverse events.
④ There are issues in administering the investigational product to the subject.
⑤ The subject is lost to follow up.
⑥ The subject has taken a prohibited concomitant medication, or it is determined necessary to administer a prohibited concomitant medication.
⑦ The subject has become pregnant during the clinical study.
⑧ Other cases in which the sponsor or the investigator determines that conducting the clinical study is not appropriate

For other matters related to the administration schedule of the investigational product, whether to drop out a subject will be determined based on the criteria described below.
A violation of the drug administration schedule will be treated as a minor protocol violation up to 5 times, and it will not be a condition for dropping out a subject within this limit. However, if it exceeds 5 times, the subject will be dropped out. The administration window of the drug for the first 4 weeks will be ±3 days (however, excluding Visit 2), and thereafter, the window will be ±5 days for the biweekly administration days. If the window of the administration day is exceeded, it will be treated and recorded as a minor violation. If the window has passed, the corresponding drug administration will be skipped and an injection will be given at the next administration day that was originally scheduled. If an injection is given before reaching the window of the administration day (e.g., at -6 days), the schedule will be adjusted by moving all subsequent administration days forward by one week. If the subject arrives at the visit day for the PSP-rating scale evaluation without 12 hours of off-medication for oral drugs that are being taken, the evaluation will be performed in that state, but it will be recorded as a minor protocol violation. However, the off-medication evaluation rules shall be followed for the remaining visit days.

5.5.3. Protocol Violations

The principal investigator and staff members of this clinical study shall fully understand and thoroughly implement the protocol to prevent violations of the protocol. To comply with the administration and test schedule of the investigational product in this clinical study, the site staff shall provide written notifications or make telephone calls regarding the study site visit schedule to allow the subjects to make visits on the applicable days without omission. However, protocol violations that occur unavoidably will be handled as shown below.

In the case of major protocol violations, the corresponding subject will be dropped out from the analysis (excluded from the per-protocol set) as a rule, and the applicable situations are as follows:
① Informed consent form was not obtained.
② The inclusion/exclusion criteria were violated.
③ Prohibited concomitant medications were administered during the clinical study.
④ The PSP-rating scale test of Visit 1 (screening), which is the first visit of this study, and Visit 16 (Week 26) were missed.

Other minor protocol violations that are judged as having no impact on the interpretation of the clinical study results will be included in the per-protocol set analysis by accurately describing the extent of violation or delay and the reason, and comprehensively considering whether the clinical study has been affected through a blind meeting prior to database lock.

5.5.4. Handling of Dropouts and Protocol Violations

Any of these situations shall be documented in the subjects' case report forms and source documents. For subjects who have been dropped out, the relevant reason will be recorded in the Clinical Trial Completion section of the case report form. Even if a subject has been dropped out, the results of previous tests shall be included in the analysis.
In the case of a subject who has been dropped out because of an adverse event, the subject will be followed up

until the subject recovers to the state prior to investigational product administration or to the baseline, or until the principal investigator can determine that the adverse event has normalized.
After randomization, subjects who discontinue participating in the clinical study or drop out, regardless of the reason, shall not be replaced.

6. Details of Clinical Study Design

6.1. Clinical Study Duration

Approximately 24 months from the approval date of the Ministry of Food and Drug Safety and the Institutional Review Board (IRB) of the study site
Subject enrollment duration: Approximately 10 months

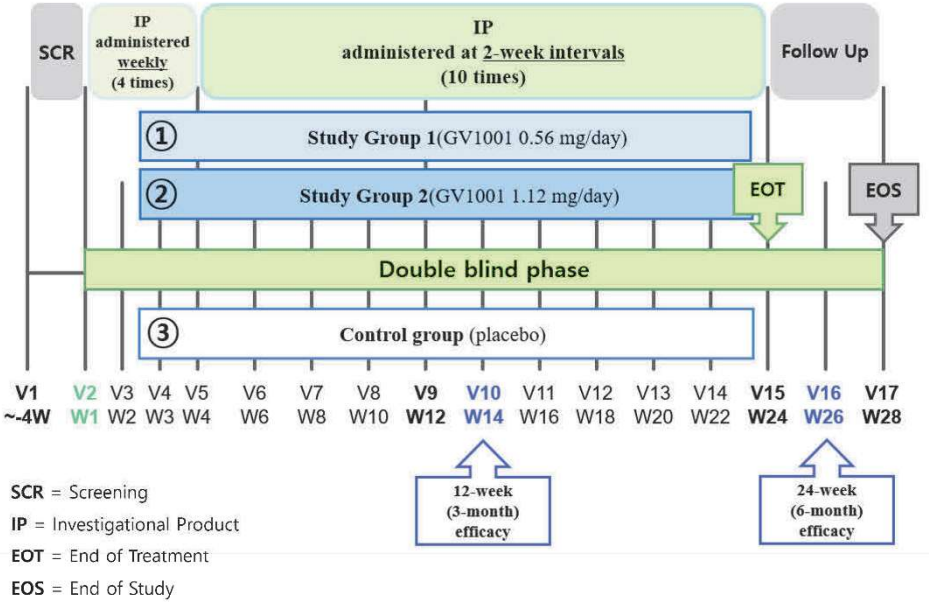
- Duration of participation for each subject: Approximately 8 months (32 weeks in total—4 weeks for screening, 24 weeks for treatment, 4 weeks for safety follow-up)
- Data management, statistical analysis, and completion of clinical study report after the end of study: Approximately 6 months

However, the planned duration of study may be extended or shortened depending on the speed of subject enrollment, changes in the procedures after the end of study, etc.

6.2. Design of Clinical Study

This is a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel design, prospective, Phase 2a exploratory clinical study.

If the subject and/or the subject's representative provide a written consent to participate in this clinical study, the required examinations and tests will be performed at the screening visit, and the screening period will run for 4 weeks or shorter.
Subjects who are ultimately determined as eligible by the inclusion/exclusion criteria after screening will be randomized at a 1:1:1 ratio to Study Group 1 (GV1001 0.56 mg/day), Study Group 2 (GV1001 1.12 mg/day), or the placebo group depending on the study site in which they are enrolled. Depending on the randomization results, subjects will be administered the investigational product (study drug or placebo) once weekly for the first 4 weeks (1 month), and then administered 10 times at 2-week intervals for 20 weeks (5 months) for a total of 14 doses over 24 weeks (6 months).
All subjects will visit the study site according to the planned clinical study schedule to receive the investigational product and to be evaluated for efficacy and safety. To ensure the objectivity and accuracy of the study results, the efficacy evaluators evaluating the PSP-rating scale will be limited to neurologists who have been sufficiently educated and trained, and the collection of efficacy and safety evaluation data and biomarkers will be performed in a consistent order at each visit.
※ Neurological drugs administered at a stable dose for at least 1 month prior to a subject's participation in this clinical study (prior to screening) will be continued without changing the dose during the clinical study participation period.



[Clinical Study Schematic]

6.3. Randomization

Subjects who provide a written consent to participate in this clinical study will be assigned a screening number consisting of [study site number: 2 digits]-S-[serial number: 3 digits] in the order in which the written consent was obtained. Subjects who meet the inclusion and exclusion criteria will then be randomized according to the randomization plan, and will be assigned a unique randomization number consisting of [study site number: 2 digits]-R-[serial number: 2 digits] in the order in which the investigator decided to enroll the subjects. Subjects who meet the inclusion and exclusion criteria will be assigned sequentially according to the order of randomization at each study site.

A randomization table will be generated by an independent statistician not related to this clinical study prior to the start of the clinical study by using SAS® (Version 9.4 or higher; SAS institute, Cary, NC, USA), and the table will be generated to allow assignment of subjects to Study Group 1, Study Group 2, or the control group at a 1:1:1 ratio by applying a stratified block randomization method. Subjects who are enrolled in this clinical study and ultimately determined to be eligible to participate in the clinical study will be assigned a randomization number sequentially through the Interactive Web Response System (IWRS), and afterward, the subjects will be assigned to Study Group 1, Study Group 2, or the control group and receive a unique IP number.

6.4. Blinding and Unblinding

To maintain double-blinding, a placebo that is indistinguishable from the investigational product in appearance will be used in this clinical study. In addition, the exterior of the investigational product container will be masked using an opaque plastic cover and sticker, and a label will be affixed on the surface to ensure that double-blinding is strictly maintained. However, to minimize the possibility of unblinding the investigator and the subjects in the management, transfer, preparation (diluting lyophilized powder in normal saline), and administration processes of the investigational product at the study site, the management of the investigational product shall be conducted as described below.

- For each study site, a clinical trial pharmacist who manages the investigational product, a person in charge of diluting the investigational product, and a person in charge of administration will be designated in advance.
- Dilution and administration of the investigational product may only be performed by a designated individual, and the person in charge of dilution and administration should be distinguished.
- The person in charge of dilution and administration shall be trained in advance on the dilution and management of the investigational product and shall have a training log.

Furthermore, to maintain double-blinding, the details of assigning unique codes to each group will not be disclosed until the end of the clinical study.
The details of assigning unique codes to each group will be managed by the Interactive Web Response System (IWRS) of the central registration center. In principle, the randomization codes shall maintain a blinded state for the treatment group assignment of each subject until the database lock is completed after the end of the clinical study (completion of the blinded study period for all subjects or dropping out of all subjects).

Double-blinding may be unblinded in the case that viewing of the relevant codes is inevitably necessary due to the occurrence of emergency situations such as serious adverse drug reactions, or if the sponsor determines that it is absolutely necessary for the rights, interests, and safety of the subjects. When double-blinding is unblinded, management will be conducted to allow only the viewing of the unique codes of relevant subjects.

Unblinding shall be considered on a case-by-case basis and only in the event of a serious medical emergency. In general, blinding shall be unblinded only if the information on the treatment group affects the subjects' treatment. If the principal Investigator or the sponsor deems it is necessary to unblind, the sponsor or the principal investigator will be contacted to obtain consent for unblinding, and then the principal investigator or the sponsor

will unblind. In this case, the unblinding will be recorded and kept as a document. Subjects whose randomization codes have been unblinded may not continue in this clinical study and will be handled as dropouts.

7. Criteria for Study Termination and Early Discontinuation

7.1. Termination Criteria

When the procedures of Visit 16 (Week 26), which is the subjects' Week 24 (6 months) efficacy evaluation visit, are completed after starting investigational product administration, this clinical study will be deemed completed. However, if there are adverse events that have not disappeared at Week 24 weeks (6 months), safety follow-up will be performed until Week 28 (7 months) thereafter, or if possible, until the corresponding adverse events disappear. This will be conducted either by the subject visiting the study site in person or by the investigator or the investigator's delegatee calling the subject over the telephone to collect relevant information such as whether the adverse event has disappeared and the date of resolution.
The termination visit of the last enrolled subject is defined as the end of the entire clinical study.

7.2. Discontinuation or Early Termination of Clinical Study

7.2.1. Sponsor

If the study site, investigator, or the sponsor's delegatee fails to comply with basic obligations, including the Korean Good Clinical Practice (KGCP), the protocol, the contract terms, and relevant laws and regulations, the sponsor shall immediately make corrections and takes actions. In the case that the following should occur, the sponsor may decide to early discontinue the entire clinical study or the clinical study at specific study sites.

1) There is a failure to enroll the target number of subjects at all or specific study sites.
2) Efficacy/safety data have emerged that can significantly affect the continuation of the clinical study.
3) The extent of violation committed by the study site or the investigator with regard to the KGCP, protocol, contract terms, and relevant laws and regulations has caused issues with the continuation of the clinical study.
4) Other administrative reasons that can have a significant impact on the continuation of the clinical study

In the case that the clinical study is terminated early or discontinued, the sponsor shall promptly report the relevant facts and reasons in writing to the principal investigator and the Minister of Food and Drug Safety, and in the case of a multicenter clinical study, the relevant facts and reasons shall also be notified in writing to the principal investigators of other study sites.

7.2.2. Investigator

If the sponsor terminates or discontinues the clinical study early, the principal investigator shall immediately notify this fact to the Institutional Review Board, submit a detailed statement of reasons for early termination and discontinuation, and also immediately notify the subjects and ensure that appropriate actions are taken and follow-ups are conducted.

If the principal investigator intends to terminate or discontinue the clinical study early, the principal investigator shall inform the sponsor in advance, immediately notify the Institutional Review Board of the decisions and the reasons, and submit a detailed statement of reasons for early termination and discontinuation.

8. Information on and Management of Investigational Product

8.1. Ingredients, Content, Dosage Form, etc., of Investigational Product

In this clinical study, 2 dose levels of a study drug (GV1001) and a comparator (placebo) are used as the investigational product. To make it impossible to distinguish in appearance, the same container (vial) will be used, and the exterior of the investigational product container will be masked using an opaque plastic cover and a sticker, and a label will be affixed on the surface to ensure that double-blinding is strictly maintained.

8.1.1. Study Drug 1: GV1001 [redacted] mg/vial

Product Code Name	GV1001 [redacted] mg/vial
Active Ingredient and Content	[redacted]
Appearance and Dosage Form	
Excipients	
Vial	
Legal Manufacturer	
Manufacturer	
Storage Conditions	Store in a sealed container at -25 to -15°C (frozen)
Storage Method after Dilution	The solution should be administered as soon as possible within a maximum of 6 hours after dilution, and it should be refrigerated at 2 to 8°C until administration.
Shelf Life	36 months from the date of manufacture (if stored frozen)

8.1.2. Study Drug 2: GV1001 [redacted] mg/vial

Product Code Name	GV1001 [redacted] mg/vial
Active Ingredient and Content	[redacted]
Appearance and Dosage Form	
Excipients	
Vial	
Legal Manufacturer	
Manufacturer	
Storage Conditions	Store in a sealed container at -25 to -15°C (frozen)
Storage Method after Dilution	The solution should be administered as soon as possible within a maximum of 6 hours after dilution, and it should be refrigerated at 2 to 8°C until administration.
Shelf Life	36 months from the date of manufacture (if stored frozen)

8.1.3. Comparator: Placebo of GV1001

Product Code Name	GV1001 Placebo
Active Ingredient and Content	None

Appearance and Dosage Form	None
Excipients	None
Vial	[redacted]
Legal Manufacturer	
Manufacturer	
Storage Conditions	Same as study drug
Storage Method after Dilution	Same as study drug
Shelf Life	Same as study drug

8.2. Packaging and Labeling of Investigational Product

The investigational product (study drug) will be manufactured or purchased by the sponsor, and then supplied to the clinical trial pharmacist at the study site.

The formulation produced as the placebo of the investigational product (hereinafter referred to as the drug) shall be identical in shape and appearance to each drug with no observable differences, and the weight difference shall not be significant. In addition, the same label shall be affixed to ensure that blinding is maintained for the subjects and the investigator.
The description on the investigational product label is provided in "Regulations on the Manufacture and Quality Control for Drugs Appendix 11. Preparation of Investigational Product," and the following will be written.

1. A phrase stating that it can only be used for clinical study purposes (e.g., "for clinical trial use only")
2. Name of the investigational product or an identification mark
3. Batch number or code number that can identify the contents and packaging operation
4. Name, address, and telephone number of the sponsor (IND holder)
5. Shelf life (effective period)
6. Storage conditions
7. Reference code that can identify the clinical study
8. If necessary, the subject identification number, drug number (treatment number), visit number, investigator's name, method of use

However, if the primary packaging container is too small to have all of the above items listed, only the minimum description information (investigational product name or identification mark/batch number or code number/sponsor's name/reference code/drug number/shelf life) shall be indicated on the label for the primary packaging according to the "Regulations on the Manufacture and Quality Control for Drugs Appendix 11," and all items shall be indicated starting on the secondary packaging.

8.3. Dosage, Administration Method, and Administration Period

[redacted]

Administration method for the study drug and the placebo

Take [redacted] mL from the vial of the study drug or the placebo and administer subcutaneously. The solution should

be administered as soon as possible within a maximum of 6 hours after dilution, and it should be refrigerated at 2 to 8°C until administration.
It is recommended to use a [redacted] mL unibody syringe for the administration of GV1001. If the injection is too shallow, loss of drug will occur at the injection site during the injection or after removing the needle.

Administration period of the study drug and the placebo

The study drug or the placebo will be administered once weekly for the first 4 weeks (1 month), and then administered 10 times at 2-week intervals for 20 weeks (5 months) for a total of 14 subcutaneous doses over 24 weeks (6 months).

8.4. Acquisition and Dispensing Management, Collection, and Disposal of Investigational Product

1) The investigational product (study drug and placebo) shall be stored in a frozen (-25 to -15°C) and sealed container, and it shall not be used without the instruction (prescription) of the principal investigator and the person in charge.
2) The sponsor shall directly deliver the investigational product, etc., to the clinical trial pharmacist after consulting the principal investigator and shall obtain and keep a certificate of receipt.
3) The clinical trial pharmacist shall store and manage the investigational product, etc., to ensure that they are not used for purposes other than the clinical study. The clinical trial pharmacist shall perform tasks such as receiving the investigational product, inventory management, administration by subject, and return, as well as record relevant information and regularly notify the principal investigator of the relevant information.
4) The sponsor shall check the quantity and storage conditions of the investigational product, etc., during the clinical study and take actions to ensure that the clinical study is conducted appropriately.
5) The sponsor shall collect and dispose of unused investigational products, etc., in the case that the clinical study is discontinued or terminated, or issues occur in the investigational product, or the shelf life or expiration date is exceeded. In such cases, the clinical trial pharmacist shall return the unused investigational products to the sponsor and a certificate of their return shall be kept.
6) The container of the investigational product dispensed to and used by the subjects during the clinical study shall be disposed of immediately after administration of the investigational product at each study site in accordance with the regulations of the respective study sites. In case of disposal, the relevant records shall be kept.

9. Administration Plan

9.1. Administration and Treatment Schedule

For 24 weeks (6 months) according to the randomization results, this clinical study will administer GV1001 0.56 mg/day for Study Group 1, GV1001 1.12 mg/day for Study Group 2, and a placebo of GV1001 for the control group once weekly for the first 4 weeks (1 month), and thereafter 10 times at 2-week intervals for 20 weeks (5 months) for a total of 14 subcutaneous doses over 24 weeks (6 months).
See section 8.3 Dosage, Administration Method, and Administration Period for details.

9.2. Permitted Concomitant Medications

Since there is no treatment that has been clearly proven to improve the symptoms of progressive supranuclear palsy, which is the target disease of this clinical study, it is considered that there will be few concomitant medications that have a significant effect on the determination of efficacy of the study drug. However, as a rule, anti-parkinsonian drugs that were being administered orally and cognitive function-improvement drugs that were being administered orally or transdermally, shall be maintained at the same dose during the clinical study. All other drugs prescribed symptomatically, such as for gastrointestinal disorders, pain, and colds, will be permitted

in the case that a change in the dose or regimen is required, discontinuation of administration is necessary, or new administration is needed. The rules for permitted concomitant medications are further summarized below.

① Concomitant medications that the subject has been taking prior to participating in this clinical study that are considered to not affect the interpretation of the results of this clinical study will be permitted based on judgment of the clinical study doctor.
② Drugs used temporarily for the treatment of other diseases or adverse events shall be concomitantly administered after a discussion with the investigator.
③ Dopaminergic drugs that were being taken at a stable dose for at least 1 month prior to the screening visit shall be taken without changing the dose during the clinical study.
④ When administering any concomitant medication (including drugs for treatment of other diseases or adverse events), the information on the corresponding drug (product name, purpose of administration, dose administered, administration period, etc.) will be recorded in detail in the case report form.

9.3. Contraindicated Concomitant Medications

The medications listed below are prohibited from concomitant administration during the clinical study.
① All investigational drugs or medical devices not specified in this clinical study
② Abuse of any drugs (including, but not limited to, illegal amphetamines, cannabis, cocaine, illegal opiates, propoxyphene, methadone, methaqualone, phencyclidine, or illegal barbiturates)
③ Regular use of narcotics (3 days a week or more)
④ Administration of other drugs that affect the immune system (immunosuppressants, oral or parenteral steroids, etc.)
⑤ Anticancer drugs

9.4. Drugs Requiring Precautions

The following drugs may be taken during the clinical study, but they shall be administered with caution, and the information on the corresponding drug (product name, purpose of administration, dose administered, administration period, etc.) shall be recorded in detail in the case report form.

① Anticholinergic drugs, amantadine, levodopa, dopamine agonists: These are allowed if the same stable dose was maintained for at least 1 month prior to screening, but if a dose adjustment is required during the clinical study, the reason as well as the detailed dose and regimen will be recorded. However, at the visits requiring an evaluation of the PSP-rating scale, the subject shall make the visit in a 12-hour off-medication state. Other cognitive evaluations or efficacy evaluations will be performed at least 1 hour after taking the drug.

② Drugs known to affect the central nervous system such as hypnotics (short-acting hypnotics: zolpidem, brotizolam lormetazepam, rilmazafone, zopiclone, ramelteon), anticonvulsants, atypical antipsychotics (seroquel, cacepin, etc.), anti-anxiety drugs (benzodiazepines [chlordiazepoxide, diazepam, alprazolam, lorazepam], buspirone, hydroxyzine), antidepressants (tricyclic antidepressants, antidepressants other than MAO inhibitors, selective serotonin reuptake inhibitors [SSRIs], etc.) (However, benzodiazepines for tests such as CTs or MRIs at visits are acceptable.)

③ Vitamin E, Ginko biloba extracts, estrogen, and brain function-improvement drugs (citicoline, oxiracetam, piracetam, acetyl-L-carnitine, nimodipine, etc.) may be used during the clinical study intermittently at low a low dose for a short term (use for less than 2 consecutive months) without changing the dose and regimen if they were being administered at a stable dose since 4 week prior to study drug administration.

9.5. Drug Compliance

The drug compliance of the investigational product is based on the number of times the study drug and the placebo

of the study drug should be administered during the clinical study.

$$\text{Drug compliance (\%)} = \frac{\text{Actual number of doses administered}}{\text{Number of doses that should be administered}} \times 100$$

10. Clinical Study Procedures and Evaluations

10.1. Clinical Study Schedule

Period	Screening	Double blind treatment phase														Follow Up	
Week	~ -4	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 EOT	16	☎ 17 EOS
Visit window (days)	-	-	±3			±5										±5	±5
Subject Consent and Assignment of Screening Number	○																
Demographic Information	○																
Checking Medical/Surgical History	○	○															
Checking prior/concomitant medications	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Physical examination	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Vital signs	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	
Weight	○	○				○				○						○	
Height	○																
Electrocardiography[1]	○									○						○	
Laboratory tests[2]	○	○				○				○						○	
Urine hCG[3]	○	○				○		○		○		○		○		○	
Checking inclusion/exclusion criteria	○	○															
Randomization		○															
K-MMSE[4]	○																

Period		Screening	Double blind treatment phase														Follow Up	
Week		~-4	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 EOT	16	☎ 17 EOS
Visit window (days)		-	-	±3			±5										±5	±5
PSP-rating scale		○									○						○	
MoCA-K			○								○						○	
K-FAB			○								○						○	
ES ADL			○								○						○	
Brain CT[5]		(○)																
Collecting human-derived samples[6]	DNA, Plasma, Serum	○									○						○	
	Cerebrospinal fluid	○															○	
Investigational product administration[7]			○	○	○	○	○	○	○	○	○	○	○	○	○	○		
Adverse Event Assessment[8]			○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

[1] Electrocardiography: For the Visit 1 (screening) test, the results of a test performed within 3 months may be used if available, and retesting may be performed only once at the discretion of the investigator.

[2] Laboratory tests: For the Visit 1 (screening) tests, the results of tests performed within 4 weeks may be used if available, and retesting may be performed only once at the discretion of the investigator. At Visit 1 (screening), the serum FSH tests shall be performed to confirm menopause in women aged ≥41 years to <55 years who have experienced amenorrhea for more than 1 year.

· Hematology test: WBC, RBC, Hemoglobin, Hematocrit, Platelets count, WBC differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)

· Blood chemistry test: BUN, Creatinine, Uric acid, Total bilirubin, Albumin, Total Protein, ALT, AST, γ-GTP, Alkaline phosphatase, Glucose, Total Cholesterol, HbA1c (performed only at screening visit)

· Serum Follicle Stimulating Hormone test: FSH (Performed only at screening visit for those who require confirmation of menopause)

· Urinalysis: Protein (Albumin), Glucose, Ketones, WBC, Blood (RBC)

· Blood coagulation test: INR (performed only at screening visit)

· Thyroid test: TSH, free T4 (performed only at screening visit)

· Syphilis, AIDS tests: VDRL or RPR, anti-HIV (performed only at screening visit)

· Serum creatinine clearance will be confirmed using the Cockcroft-Gault formula. (performed only at screening visit)

CLcr = [(140 − Age (years)] × Weight (kg) × 0.85 (for female subjects) / 72×Serum Creatinine (mg/dl)

[3] Urine hCG: Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal. However, for Visit 1 (screening), the subjects who performed the serum FSH test to confirm menopause when participating in the clinical study will also perform the urine hCG pregnancy test.

[4] K-MMSE: The results of a test performed at the study site within 2 weeks prior to the screening visit may be used if available.
[5] Brain CT: This will be performed only on subjects without brain CT imaging within 12 months prior to the screening visit.
[6] Collecting human-derived samples: Human-derived samples (DNA, plasma, serum, and cerebrospinal fluid) will be collected for exploratory evaluations, and they will be transferred to the central lab for analysis and storage. However, in the case of cerebrospinal fluid, it will be collected only from subjects who have separately consented to collection of samples. For Visit 1 (screening), separate visits for collecting human-derived samples can be set up and implemented within the screening period.
[7] Investigational product administration: Subjects will be observed for approximately 20 minutes after the administration of the investigational product from Visit 2 to Visit 15.
[8] Adverse event assessment: Adverse events that occurred after the first administration of the investigational product will be identified, and prior to the first administration, it will be collected as medical history.

10.2. Evaluation Items by Visit

10.2.1. Visit 1 (Screening, From -4 Weeks)

After the consent procedures of the subject and/or the subject's representative are completed and the written informed consent form is obtained, the following evaluations will be performed after the screening number is assigned. However, a written consent may be obtained prior to Visit 1 (screening), and the tests that could not be performed at Visit 1 (screening), they may be performed at a revisit within the screening period.

- The demographic information of the subject, medical/surgical history, and prior/concomitant drug administration history will be investigated.
- A physical examination will be performed.
- Vital signs will be measured.
- Weight and height will be measured.
- Electrocardiography will be performed.
  (However, the results of a test performed within 3 months may be used if available, and retesting may be performed only once at the discretion of the investigator.)
- Laboratory tests will be performed.
  (However, the results of tests performed within 4 weeks may be used if available, and retesting may be performed only once at the discretion of the investigator. The serum FSH tests shall be performed to confirm menopause in women aged ≥41 years to <55 years who have experienced amenorrhea for more than 1 year.)
- Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.
  (However, the subjects who performed the serum FSH test to confirm menopause when participating in the clinical study will also perform urine hCG pregnancy test.)
- The inclusion/exclusion criteria will be checked.
- The K-MMSE test will be performed.
  (However, the results of a test performed at the study site within 2 weeks prior to the screening visit may be used if available.)
- The PSP-rating scale test will be performed.
- A brain CT will be performed only on subjects without brain CT imaging within 12 months prior to the screening visit.
- Human-derived samples (DNA, plasma, serum, cerebrospinal fluid) will be collected for exploratory evaluations. However, in the case of cerebrospinal fluid, it will be collected only from subjects who have separately consented to collection of samples. Separate visits for collecting human-derived samples can be set up and implemented within the screening period.
- The date of the next visit will be designated.

10.2.2. Visit 2 (Randomization and Baseline, Week 1)

This visit will occur within 4 weeks after Visit 1 (screening, initial visit date), and the evaluations that should be performed at this visit are as follows:

- Changes in the medical/surgical history and prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.

- Weight will be measured.
- Laboratory tests will be performed.
- Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.
- The results of all tests and evaluations including the screening visit thus far will be combined to finally evaluate whether the subjects who meet the inclusion/exclusion criteria have been included.
- Randomization numbers will be assigned by performing randomization.
- The MoCA-K test will be performed.
- The K-FAB test will be performed.
- The ES ADL test will be performed.
- The investigational product will be administered.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.3. Visits 3 to 5 (Weeks 2, 3, and 4 ± 3 days)

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The investigational product will be administered after confirming that the clinical study can be continued.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.4. Visits 6 (Weeks 6 ± 5 days)

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- Weight will be measured.
- Laboratory tests will be performed.
- Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.
- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The investigational product will be administered after confirming that the clinical study can be continued.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.5. Visits 7 to 9 (Weeks 8, 10, 12 ± 5 days)

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- **For Visit 8 only,** urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.
- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The investigational product will be administered after confirming that the clinical study can be continued.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.6. Visit 10 (Week 12 [3 months] Efficacy Evaluation, Week 14 ± 5 days)

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- Weight will be measured.
- Electrocardiography will be performed.
- Laboratory tests will be performed.
- Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.
- The PSP-rating scale test will be performed.
- The MoCA-K test will be performed.
- The K-FAB test will be performed.
- The ES ADL test will be performed.
- Human-derived samples (DNA, plasma, serum) will be collected for exploratory evaluations.
- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The investigational product will be administered after confirming that the clinical study can be continued.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.7. Visits 11 to 14 (Weeks 16, 18, 20, and 22 ± 5 days)

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- **For Visit 12 and Visit 14 only,** urine hCG pregnancy tests will be performed only for women of

childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.

- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The investigational product will be administered after confirming that the clinical study can be continued.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.8. Visit 15 (End-of-Treatment Visit; Week 24 ± 5 days)

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The investigational product will be administered after confirming that the clinical study can be continued.
- The subjects will be observed for adverse events for approximately 20 minutes after investigational product administration.
- The date of the next visit will be designated.

10.2.9. Visit 16 (Week 24 [6 months] Efficacy Evaluation, Week 26 ± 5 days)

At this visit, the Week 24 (6 months) efficacy evaluation will be performed.

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- A physical examination will be performed.
- Vital signs will be measured.
- Weight will be measured.
- Electrocardiography will be performed.
- Laboratory tests will be performed.
- Urine hCG pregnancy tests will be performed only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal.
- The PSP-rating scale test will be performed.
- The MoCA-K test will be performed.
- The K-FAB test will be performed.
- The ES ADL test will be performed.
- Human-derived samples (DNA, plasma, serum, cerebrospinal fluid) will be collected for exploratory evaluations. However, in the case of cerebrospinal fluid, it will be collected only from subjects who have separately consented to collection of samples.
- The occurrence of adverse events after the administration of the investigational product at the previous visit and their details will be investigated.
- The date of the next telephone visit will be scheduled.

10.2.10. Visit 17 (End-of-Study Visit, Week 28 ± 5 days)

This is the study termination visit, which will be conducted over the telephone.

- Changes in the prior/concomitant drug administration history will be checked compared with the previous visit.
- The occurrence of adverse events since the previous visit and their details will be investigated.

10.2.11. Unscheduled Visits

Additional visits may be made from time to time, outside of the scheduled visits, at the request of the subject or the subject's representative or as deemed necessary based on the judgment of the investigator. To this end, the investigator shall inform the subjects of this during their regular visits to the study site, and ensure that the subjects immediately contact the investigator if any adverse events should occur. The visit schedule shall not be changed because of the unscheduled visits. At unscheduled visits, examinations and tests may be performed at the discretion of the investigator.

10.3. Evaluation Methods

10.3.1. Subject Consent and Assignment of Screening Number

The investigator will explain this clinical study to the subject in detail, answer questions asked by the subject, and request the subject to participate in the clinical study. If the subject consents to participate in the clinical study, a written consent will be obtained from the subject (or the subject's representative). A screening number will be assigned in the order in which the written consent is obtained.
A written consent will be obtained from the subject's guardian as well when consent is obtained from the subject. The guardian and the subject's representative may be the same or different (even if the guardian and the subject's representative are the same, the guardian's written consent shall be obtained separately).

10.3.2. Demographic Information

The subject's name, initials, sex, month and year of birth, age, etc., will be investigated.

10.3.3. Checking Medical/Surgical History

The subject's medical history will be investigated in detail and recorded through an interview and a review of past medical records. History of operations, surgical history, allergy history, etc., within the 6 months prior to screening (however, for malignant tumors [cancers], the history within 5 years prior to screening will be checked), present illness, presence or absence of hypersensitivity reactions, time of occurrence (year or month of occurrence), and persistence at screening will be recorded.

10.3.4. Checking Prior/Concomitant Medications

History of drug administration within 4 weeks from Visit 1 (screening) and administration status (product name, purpose of administration, dose administered, administration period, etc.) will be investigated. However, in the case of the administration history of this investigational product to check the exclusion criteria, the administration history within 12 months prior to screening will be investigated.
By comparing the details confirmed in the investigation of the drug administration history at screening, the changes at subsequent visits will be investigated, and if there are changes in the concomitant medications, the relevant information shall be recorded in detail in the source documents.

10.3.5. Physical Examination

At all visits, a physical examination through inspection, palpation, percussion, and auscultation will be performed

for each subject to check the subject's health status and to check for any adverse events. The physical examination will include appearance, skin, head/neck, chest/lungs, heart, abdomen, urinary/genital system, extremities, musculoskeletal system, nervous system, and lymph nodes.

10.3.6. Vital Signs

Blood pressure, pulse, respiratory rate, and body temperature will be measured as vital signs. This shall be performed prior to the planned tests as much as possible according to the clinical study schedule, and measurements shall be taken in a sitting position after 5 minutes of rest.

10.3.7. Weight and Height

Height will be measured only at Visit 1 (screening), and weight will be measured at Visit 1 (screening) and at each time point thereafter according to the set schedule. Weight will be measured after taking off outerwear and shoes and emptying the pockets, and the same weight scale will be used whenever possible when measuring weight.

10.3.8. Electrocardiography

For the ECG (12-lead electrocardiogram) of Visit 1 (screening), the results of a test performed within 3 months may be used if available, and retesting may be performed only once at the discretion of the investigator.

10.3.9. Laboratory Tests

For the laboratory tests of Visit 1 (screening), the results of tests performed within 4 weeks may be used if available, and retesting may be performed only once at the discretion of the investigator. If retesting is performed, the final checking of the inclusion/exclusion criteria will be based on the results of retesting.

Among the blood chemistry test items, HbA1c and coagulation tests, thyroid test, syphilis, acquired immune deficiency syndrome (AIDS) test, and creatinine clearance test will be performed only at Visit 1 (screening). At Visit 1 (screening), the serum FSH tests shall be performed to confirm menopause in women aged ≥41 years to <55 years who have experienced amenorrhea for more than 1 year.

Hematology test	White blood cell (WBC), Red blood cell (RBC), Hemoglobin, Hematocrit, Platelets count, WBC differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
Blood chemistry test	Blood urea nitrogen (BUN), Creatinine, Uric acid, Total bilirubin, Albumin, Total Protein, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), γ-Glutamyl transpeptidase (GTP), Alkaline phosphatase, Glucose, Total Cholesterol, HbA1c (performed only at screening visit)
Serum Follicle Stimulating Hormone test	FSH (Performed only at screening visit for those who require confirmation of menopause)
Urinalysis	Protein (Albumin), Glucose, Ketones, WBC, Blood (RBC)
Blood coagulation test	International normalized ratio (INR) (performed only at screening visit)
Thyroid test	Thyroid stimulating hormone (TSH), free T4 (performed only at screening visit)
Syphilis, AIDS tests	Venereal disease research laboratory (VDRL), or Rapid plasma reagin (RPR), anti-HIV (performed only at screening visit)
Creatinine clearance	This will be confirmed using the Cockcroft-Gault formula. (performed only at screening visit) CLcr = [(140 − Age (years)] × Weight (kg) × 0.85 (for female subjects) / 72 × Serum Creatinine (mg/dl)

10.3.10. Urine hCG

Pregnancy will be checked with a urine human chorionic gonadotropin (hCG) response test only for women of childbearing potential, excluding subjects confirmed to have undergone surgical sterilization and as being menopausal. However, for Visit 1 (screening), the subjects who performed the serum FSH test to confirm menopause when participating in the clinical study will also perform the urine hCG pregnancy test.

Women of childbearing potential are defined as individuals who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not menopausal.
In this clinical study, menopause is defined as one or more of the following.

(1) Female subjects aged ≥55 years who have had amenorrhea for more than 1 year
(2) Female subjects aged ≥41 years to <55 years who have had amenorrhea for more than 1 year and have a serum follicle stimulating hormone (FSH) level ≥ 30 mIU/mL
(3) In case of artificial menopause caused by bilateral oophorectomy

10.3.11. K-MMSE

The Korean Mini-Mental State Examination (K-MMSE) will be used to screen subjects for cognitive function at Visit 1 (screening). However, the results of a test performed at the study site within 2 weeks may be used if available.
The K-MMSE consists of "orientation," "memory registration," "attention and calculation," "memory recall," and "verbal ability and visuospatial organizing ability." The score range is from 0 to 30, with greater cognitive impairments resulting in lower scores.[17)]
See [Appendix 4]. K-MMSE for details.

10.3.12. PSP-rating scale

The PSP-rating scale evaluation will be performed at Visit 1 (screening), Visit 10, and Visit 16, and the baseline of the PSP-rating scale shall be Visit 1 (screening). At the visits requiring an evaluation of the PSP-rating scale, the subject shall make the visit in a 12-hour off-medication state for the oral drugs specified in advance. This is corresponds to a neurological examination that is directly evaluated by a neurologist who has received or is receiving a subspecialty training on dyskinesia, and the scores are summed according to a set form.[14, 33)]
See [Appendix 5]. PSP-rating scale for details.

10.3.13. MoCA-K

The Montreal Cognitive Assessment-Korean version (MoCA-K) will be used as a measure of overall cognitive function in patients with progressive supranuclear palsy. The MoCA-K test will be performed a total of 3 times at Visit 2, Visit 10, and Visit 16, and the scores will be summed according to a set form.[18)]
See [Appendix 6]. MoCA-K for details.

10.3.14. K-FAB

The Korean Frontal Assessment Battery (K-FAB) test will be used as a measure to show the extent of frontal lobe dysfunction. The K-FAB test will be performed a total of 3 times at Visit 2, Visit 10, and Visit 16, and the scores will be summed according to a set form.[19)]
See [Appendix 7]. K-FAB for details.

10.3.15. ES ADL

England & Schwab Activity of Daily Living (ES ADL) is a scale that distinguishes the overall performance of daily living in patients with Parkinson's disease, etc., from 0 (complete dependence) to 100% (complete independence) based on the level of independence. The ES ADL test will be performed a total of 3 times at Visit

2, Visit 10, and Visit 16, and the scores will be evaluated according to a set form.[20)]
See [Appendix 8]. ES ADL for details.

10.3.16. Brain CT

This will be performed only on subjects without brain CT imaging within 12 months prior to Visit 1 (screening).

10.3.17. Collecting Human-Derived Samples

Human-derived samples (DNA, plasma, serum, and cerebrospinal fluid) will be collected for exploratory evaluations, and they will be transferred to the central lab for analysis and storage.
Blood collection for DNA, plasma, and serum is performed at Visit 1, Visit 10, and Visit 16, in the case of cerebrospinal fluid, it will be collected only from subjects who have separately consented to collection of samples at Visit 1 and Visit 16. For Visit 1 (screening), separate visits for collecting human-derived samples can be set up and implemented within the screening period.
Samples collected for exploratory evaluations will be stored for 10 years from the termination date of the clinical study and then disposed of according to the regulations of the relevant study site.
The collected samples may be used for similar or comprehensive studies only if the subjects agree to provide them for secondary use in the Human-Derived Samples Consent form, and the samples collected will also be stored for 10 years from the termination date of the clinical study and then disposed of according to the regulations of the relevant study site.
Plasma protein and inflammatory response markers in blood and cerebrospinal fluid will be tested at the central lab, and the test items are as shown below. The baseline of the test results using human-derived samples shall be Visit 1 (screening).

- Total tau (t-Tau), phosphorylated tau (p-Tau), and neurofilament-light chain (NfL) in blood and cerebrospinal fluid
- Inflammatory cytokine markers (IL-6, IL-8, IL-2, IFN- γ, TNF-α, etc.) in blood and cerebrospinal fluid

10.3.18. Investigational Product Administration

This clinical study will administer GV1001 0.56 mg/day for Study Group 1, GV1001 1.12 mg/day for Study Group 2, and a placebo of GV1001 for the control group once weekly for the first 4 weeks (1 month), and thereafter 10 times at 2-week intervals for 20 weeks (5 months) for a total of 14 subcutaneous doses over 24 weeks (6 months). Observation for adverse events will be conducted for approximately 20 minutes after the administration of the investigational product from Visit 2 to Visit 15.

10.3.19. Adverse Event Assessment

Adverse events that occurred after the first administration of the investigational product will be identified, and prior to the first administration, it will be collected as medical history.

10.4. Endpoints

10.4.1. Primary Efficacy Endpoint

Change from the baseline in the total score of PSP-rating scale after 24 weeks (6 months) of investigational product administration

10.4.2. Secondary Efficacy Endpoints

1) Change from the baseline in the total score of PSP-rating scale after 12 weeks (3 months) of investigational product administration
2) Change from the baseline in the Montreal Cognitive Assessment - Korea (MoCA-K) after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
3) Change from the baseline in the Korean Frontal Assessment Battery (K-FAB) after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
4) Change from the baseline in the England & Schwab Activity of Daily Living (ES ADL) scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
5) Change from the baseline in the score of each domain of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
6) Change from the baseline in the score of each item of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration

10.4.3. Exploratory Endpoints

1) Change from the baseline in total tau (t-tau), phosphorylated tau (p-tau), and neurofilament light chain (NfL) markers in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid after 24 weeks (6 months) of investigational product administration
2) Change from the baseline in inflammatory cytokine markers (IL-6, IL-8, IL-2, IFN- γ, TNF-α, etc.) in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid after 24 weeks (6 months) of investigational product administration
3) Change from the baseline in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid markers after 24 weeks (6 months) of investigational product administration, and correlation between clinical markers and treatment responses

10.4.4. Safety Endpoints

1) Adverse events
2) Laboratory tests (hematology test, blood chemistry test, urinalysis)
3) Vital signs
4) Electrocardiogram

10.5. Definition and Reporting of Adverse Events

10.5.1. Definition of Adverse Events

(1) Adverse event (AE)

This refers to any harmful and unintended signs (including abnormal laboratory test results, etc.), symptoms, or diseases that occur in a subject who has been administered an investigational product, and it does not necessarily must have a causal relationship to the investigational product.

(2) Adverse drug reaction (ADR)

This refers to any harmful and unintended reactions that occur at any dose of an investigational product and of which the causal relationship to the investigational product cannot be denied.

(3) Unexpected adverse drug reaction

This refers to a difference in the pattern of an adverse drug reaction or the extent of harm in light of the available information on the drug such as the investigator's brochure or the product insert of the drug.

(4) Serious adverse event/adverse drug reaction (serious AE/ADR)
This refers to an adverse event or adverse drug reaction that occurs at any dose of an investigational product that corresponds to any one of the following:

① Occurrence of death or life-threatening risks
② Requires hospitalization or prolongation of hospitalization
③ Results in permanent or significant disability or functional decline
④ Occurrence of malformations or abnormalities in a fetus
⑤ Other than cases ① through ④, occurrence of drug dependence or abuse, or cases in which medically significant situations occur, such as hematopathies

However, in this clinical study, a visit made for the following reasons will not be considered as a serious adverse event.

- Hospitalization planned prior to the clinical study
- Hospitalization for medical examination, cosmetic reasons, and recuperation
- Cases in which the time of visiting the emergency room has not exceeded 24 hours. However, it may be considered a serious adverse event based on the investigator's judgment even if it does not exceed 24 hours.

If a situation occurs that is considered to have a significant impact on the patient's well-being and health status, even if not listed above, it shall be determined whether to consider it as a serious adverse event according to the medical judgment of the doctor in charge and relevant specialists, and appropriate measures shall be taken accordingly.

10.5.2. Reporting of Adverse Events

- Adverse events will be collected during the clinical study from the time point after investigational product administration and up to the final visit. All medical events that occur prior to investigational product administration will be recorded as medical history.
- Adverse events shall be reported by including the name of the adverse event, duration (start date and disappearance date), severity, causal relationship to the investigational product, actions taken for the investigational product, outcome, corrective treatment for the adverse event, and whether the event is a serious adverse event.
- When recording an adverse event, the investigator shall use a comprehensive diagnosis or symptom using standard medical terminology rather than recording each symptom or sign.
- Adverse events that occur during the clinical study shall be followed up until they disappear, show stable outcomes, or the subject is lost to follow-up.
- Adverse events that occur after the end of the clinical study shall be reported only if they are serious and related to the investigational product.

1) Severity Assessment
The investigator will assess the severity of adverse events and serious adverse events by referring to the criteria described below.

Mild	The event causes minimal discomfort without interfering with the subject's normal daily life (function), and it can be easily tolerated by the subject.
Moderate	The event causes discomfort that significantly interferes with the subject's normal daily life (function).

Severe	The event makes the subject's normal daily life (function) impossible.

Activities of daily living are defined below.
: All activities that occur in daily life to take care of one's own body (e.g., bathing, dressing and undressing, eating, taking medications, hygiene, and personal care)

An adverse event or serious adverse event can both be evaluated as severe according to the definition above, and one should not be confused for the other since a severe adverse event does not necessarily correspond to a serious adverse event.

2) Causality Assessment

The investigator will assess the causal relationship between an adverse event and the investigational product by referring to the criteria described below. If it is assessed as unlikely, it can be determined as "no causal relationship" (non-ADR). If it is assessed as other items, it will be determined that there is a causal relationship (ADR).

① Certain
The relationship between the administration and use of the drug, etc., is reasonable, and it is not explained by other drugs, chemicals, or accompanying diseases, and a clinically reasonable response is shown when administration of the drug, etc., is discontinued, and it is pharmacologically or phenomenologically conclusive when the drug, etc., is rechallenged as needed.

② Probable, likely
The chronological relationship between the administration and use of the drug, etc., is reasonable, and it does not appear to be due to other drugs, chemicals, or accompanying diseases, and a clinically reasonable response is shown when administration of the drug, etc., is discontinued (no information on rechallenge)

③ Possible
The chronological relationship between the administration and use of the drug, etc., is reasonable, but it is also explained by other drugs, chemicals, or accompanying diseases, and there is insufficient or unclear information on discontinuing administration of the drug, etc.

④ Unlikely
It is a transient case that does not seem to have a causal relationship to the administration or use of the drug, etc., and it can be reasonably explained as being caused by other drugs, chemicals, or potential diseases.

⑤ Conditional, unclassified
More data are needed for an appropriate evaluation or additional data are being reviewed.

⑥ Unassessable, unclassifiable
A determination cannot be made because the information is insufficient or contradictory, and it cannot be supplemented or confirmed.

10.5.3. Reporting of Serious Adverse Events

All serious adverse events that occur from the time point after investigational product administration and up to the final visit shall be reported to the sponsor via telephone, fax, e-mail, etc., within 24 hours of the investigator's recognition, regardless of their relationship to the investigational product, and they must be reported to the IRB of the affiliated study site within the timeline specified by the IRB.

Adverse events that occur after the end of the clinical study shall be reported only if they are serious and related to the investigational product.

When reporting serious adverse events to the sponsor, the investigator shall use the subject identification code instead of the subject's personal information such as the name, resident registration number, and address in order to protect the confidentiality of the subject's identity. Even if copies of some medical records are requested as needed, the personal information, except the identification code, will be redacted.

If the investigator becomes aware of any additional information on reported serious adverse events, a follow-up report shall be made. The investigator shall conduct follow-ups and submit reports to the sponsor and the IRB until the corresponding serious adverse event disappears, shows a stable outcome, or the subject is lost to follow-up.

10.5.4. Reporting Procedures for Suspected Unexpected Serious Adverse Reactions (SUSARs)

In the case that suspected unexpected serious adverse reactions (SUSARs) occur during the study period, the sponsor shall report them to the investigator, the Minister of Food and Drug Safety, and the IRB within the period specified in each of the following paragraphs. For details, see “Regulations on the Safety of Drugs, etc.” Appendix 4 Korean Good Clinical Practice for Drugs and the guide for civil petitioners, “Considerations for Safety Evaluation and Reporting of the Sponsor of Clinical Trial for Drugs.”

① For unexpected adverse drug reactions that result in death or are life-threatening, they shall be reported as soon as possible via telephone, fax, and documents within 7 days from the date the sponsor was initially reported of the relevant fact or became aware of it. If not all of the information was reported according to the adverse drug reaction report, a detailed report shall be additionally submitted within 15 days from the date the sponsor was initially reported of the relevant adverse drug reaction or became aware of it.
② All other SUSARs shall be reported within 15 days from the date the sponsor was reported of the relevant fact or became aware of it.

In the case that suspected unexpected serious adverse reactions (SUSARs) occur during the clinical study, the principal investigator and study staff members shall make every effort for the safety of the subjects, and take prompt and appropriate actions to minimize the adverse events. If additional information on the reported adverse drug reaction is available, the sponsor shall be report it until the corresponding adverse drug reaction is ended (refers to the disappearance of the corresponding adverse drug reaction or becoming impossible to follow up).

If the clinical study is conducted at multiple study sites, the sponsor shall promptly notify the study sites through the principal investigators.

10.6. Pregnancy

Pregnancy of a female subject during the clinical study is not considered an adverse event, and an elective abortion without complications (not applicable for therapeutic abortion) or hospitalization for live birth of a healthy newborn is also not considered an adverse event.

However, if a female subject becomes pregnant during the clinical study, the subject shall be dropped out from the clinical study, and the investigator shall complete a pregnancy report form and submit it to the clinical study sponsor within 24 hours of becoming aware of the pregnancy. In addition, even for cases in which a pregnancy is confirmed within 90 days after the end of the clinical study (discontinuation), the investigator shall complete a pregnancy report form and submit it to the clinical study sponsor within 24 hours of becoming aware of the pregnancy. The investigator shall submit follow-up reports on the subsequent progress of the pregnant woman and the fetus until birth even if the subject discontinues participation in the clinical study or completes the clinical study.

Serious maternal complications, spontaneous abortions, ectopic pregnancy, stillbirths, neonatal deaths, congenital malformations, etc., are considered serious adverse events, and the investigator shall report them according to the procedures in section 10.5.3Reporting of Serious Adverse Events.

10.7. Overdosing

Overdosing is defined as an accidental or intentional administration of a drug at a dose considered by the

investigator to be excessive and medically significant. The investigator will consider overdosing as a significant medical event and report it to the sponsor, regardless of the adverse event outcome.

11. Data Analysis and Statistical Considerations

11.1. Analysis Set

The main analysis of efficacy evaluation of this clinical study will be performed on the full analysis set (FAS), and the analysis on the per-protocol set (PPS) will be performed as a supplement. The safety evaluation analysis will be performed as actually administered in the safety set. The exploratory evaluation analysis will be performed on the FAS and PPS, and the demographic and the characteristics prior to administration will be analyzed in all randomized subjects.

11.1.1. Efficacy Evaluation Set

Full Analysis Set (FAS)
This includes subjects who received at least 1 dose of the investigational product after randomization and had at least 1 evaluation with the PSP-rating scale after the administration of the investigational product and up to the end of the clinical study.

Per-Protocol Set (PPS)
Among the subjects included in FAS, the subjects who completed the clinical study without major protocol violations are included. Subjects with major protocol violations (see 5.5.3 Protocol Violations) may be excluded from PPS.

Exclusion from PPS will be decided through a blind meeting prior to database lock, after comprehensively discussing whether the clinical study was affected.

11.1.2. Safety Evaluation Set

Safety set
Among the subjects who were administered at least one dose of the investigational product after randomization, subjects whose safety-related data were evaluated at least once after the administration will be included.

11.2. Statistical Analysis Method

11.2.1. General Principles of Analysis

All statistical analyses will use SAS® (version 9.4 or higher; SAS Institute, Cary, NC, USA). In principle, all tests are two-sided tests under a significance level of 5% unless otherwise specified. The efficacy evaluation of this clinical study will perform analysis according to the “intention-to-treat principle,” and the safety evaluation will perform analysis as actually administered. Continuous data will present the number of subjects observed, mean, standard deviation, median, minimum, and maximum, while categorical data will present frequencies and percentages by category.

11.2.2. Method of Handling Missing Data

When analyzing the efficacy endpoints and exploratory endpoints, in the case of utilizing the mixed-effect model repeated measure (MMRM) method, the available data will be analyzed as they are since the method does not require the replacement of missing values. If missing values occur in the safety endpoints and exploratory endpoints analyzed by methods other than MMRM, analysis will be performed only on the collected data without imputation.

11.2.3. Covariate Adjustment

Efficacy endpoints will be analyzed with adjustments for the baseline values as well as for the age and sex.

11.2.4. Interim Analysis

No interim analysis will be performed before the end of the clinical study. However, an interim analysis related to the safety of this clinical study may be conducted when a serious issue related to safety is discovered and the need is recognized through a meeting or a deliberation of the investigator or principal investigator.

11.2.4.1. Independent Data Monitoring Committee (IDMC)

A discussion may be held according to the charter of an independent data monitoring committee (IDMC) composed of clinical experts not including the principal investigator, sub-investigators, and sponsor to make objective decisions on details related to safety by clarifying the judgment on safety findings obtained during the course of this clinical study.

11.2.4.2. Safety Monitoring

The principal investigator will act as the protocol safety manager based on the risk level of this clinical study, and the principal investigator at each study site will monitor the safety of the subjects participating in the relevant study site in accordance with the protocol during the clinical study.
Whenever serious adverse events and adverse drug reactions occur, the principal investigator will collect and review the relevant subject's data and safety information. If adverse events, unexpected problems, and protocol noncompliance cases should occur, the principal investigator shall submit reports to the sponsor (including the CRO) and the IRB in accordance with the protocol, IRB regulations of each study site, KGCP, and relevant regulations, and also submit reports to the Ministry of Food and Drug Safety if necessary. In addition, in accordance with the criteria for early termination or discontinuation of the clinical study in section 7.2, reports will be submitted to the sponsor in a timely manner if any efficacy and safety information that can significantly impact the continuation of the clinical study should emerge, and the sponsor will discuss and decide on the continuation of the clinical study according to the sponsor's standard operating procedure (SOP).

11.2.5. Multiple Comparisons and Multiplicity

Given that this is a Phase 2 clinical study for therapeutic exploratory purposes, no correction of type I error due to comparisons with the control group were considered for each of the study groups (GV1001 0.56 mg/day, 1.12 mg/day).

11.2.6. Subgroup Analysis

Subgroup analysis will not be considered in this clinical study.

11.2.7. Demographic Information and Other Characteristics Prior to Treatment

The demographic information and other characteristics prior to treatment of the subjects included in this clinical study will be summarized by treatment group. Continuous variables will present the number of subjects observed, mean, standard deviation, median, minimum, and maximum. In addition, depending on whether the assumption of normality is satisfied, the two-sample t-test (if normality assumption is satisfied) or Wilcoxon's rank-sum test (if normality assumption is not satisfied) will be used to compare each study group with the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group). Categorical variables will present frequencies and percentages, and depending on whether cells with an expected frequency less than 5 exceed 20% of the total cells, Pearson's chi-square test (if the cells with an expected frequency less than 5 does not exceed 20% of the total cells) or Fisher's exact test (if the cells with an expected frequency less than 5 exceed 20% of the total cells) will be used to compare each study group with the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group).
Medical history will be standardized using the Medical Dictionary for Regulatory Activities (MedDRA), and the frequency, percentage, and number of cases will be presented by group for each standardized medical history. Prior/concomitant medications will be standardized by the ATC code of the WHO Drug Dictionary, and the

frequency and percentage of subjects as well as the number of cases will be presented by group for each standardized concomitant medication.

11.2.8. Efficacy Analysis

11.2.8.1. Primary Efficacy Analysis

Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in the total score of the PSP-rating scale after 24 weeks (6 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between the study groups and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group) and its 95% confidence interval as well as the two-side *p*-value.

11.2.8.2. Secondary Efficacy Analysis

1) Change from the baseline in the total score of PSP-rating scale after 12 weeks (3 months) of investigational product administration
   Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in the total score of the PSP-rating scale after 12 weeks (3 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between treatment groups and its 95% confidence interval, and the two-sided *p*-value.

2) Change from the baseline in the Montreal Cognitive Assessment - Korea (MoCA-K) after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
   Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in MoCA-K after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between treatment groups and its 95% confidence interval, and the two-sided *p*-value.

3) Change from the baseline in the Korean Frontal Assessment Battery (K-FAB) after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
   Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in K-FAB after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will

be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between treatment groups and its 95% confidence interval, and the two-sided *p*-value.

4) Change from the baseline in the England & Schwab Activity of Daily Living (ES ADL) scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in ES ADL after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between treatment groups and its 95% confidence interval, and the two-sided *p*-value.

5) Change from the baseline in the score of each domain of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in the score of each domain of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between treatment groups and its 95% confidence interval, and the two-sided *p*-value.

6) Change from the baseline in the score of each item of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration
Descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) will be presented by treatment group for the change from the baseline in the score of each item of the PSP-rating scale after 12 weeks (3 months) and 24 weeks (6 months) of investigational product administration. To test the difference between each study group and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group), an MMRM analysis will be conducted with the treatment groups, visits, and interactions between the visits and the treatment groups set as fixed effects, and the subjects set as the random effect, as well as considering the baseline values, age, and sex as covariates. The results of the MMRM analysis will be summarized by LSM and standard error (SE) for each treatment group, the LSM difference between treatment groups and its 95% confidence interval, and the two-sided *p*-value.

11.2.9. Exploratory Evaluation Analysis

1) Change from the baseline in total tau (t-tau), phosphorylated tau (p-tau), and neurofilament light chain (NfL) markers in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid after 24 weeks (6 months) of investigational product administration
2) Change from the baseline in inflammatory cytokine markers (IL-6, IL-8, IL-2, IFN- γ, TNF-α, etc.) in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid after 24 weeks (6 months) of investigational product administration
3) Change from the baseline in blood after 12 weeks (3 months), and in blood and cerebrospinal fluid markers after 24 weeks (6 months) of investigational product administration, and correlation between clinical markers and treatment responses

Appropriate statistical analyses, such as MMRM and correlation analysis, will be performed for exploratory endpoints after investigational product administration, compared with the baseline according to data characteristics such as continuous data and categorical data.

11.2.10. Safety Analysis

11.2.10.1. Adverse Events

The analysis of adverse events will be based on treatment-emergent adverse events (TEAEs). The number of subjects with onset by treatment group, the incidence, and the 95% confidence interval of the incidence will be presented for adverse events, adverse drug reactions, serious adverse events, and serious adverse drug reactions. In addition, to test the difference in the incidence of adverse events by treatment group, comparisons between groups (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group) will be performed with Pearson's chi-square test (if the cells with an expected frequency less than 5 does not exceed 20% of the total cells) or Fisher's exact test (if the cells with an expected frequency less than 5 exceed 20% of the total cells), depending on whether cells with an expected frequency less than 5 exceed 20% of the total cells Adverse events, adverse drug reactions, serious adverse events, and serious adverse drug reactions will be coded according to the system organ class (SOC) and preferred term (PT) by using MedDRA, and the number of subjects with onset, the incidence, and the number of occurrences of the coded adverse events will be presented by treatment group. In addition, the status of adverse event occurrences according to their severity and causal relationship to the investigational product will be presented.

11.2.10.2. Laboratory Tests

For the laboratory test results, continuous variables will present the test values at each visit as well as descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) for changes from the baseline by treatment group. In addition, depending on whether the assumption of normality is satisfied, the intragroup comparison will use the paired *t*-test or Wilcoxon's signed-rank test, while the intergroup comparison (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group) will use the two-sample *t*-test or Wilcoxon's rank-sum test to perform analysis. For categorical variables, shift tables will be presented by treatment group, and the intragroup comparison will use McNemar's test, while the intergroup comparison (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group) will use Pearson's chi-square test or Fisher's exact test to perform analysis.

11.2.10.3. Vital Signs

For vital signs, the measurement values at each visit as well as descriptive statistics (number of subjects observed, mean, standard deviation, median, minimum, and maximum) for the changes from the baseline will be presented by treatment group. In addition, to test the intragroup difference before and after investigational product administration, the paired *t*-test (if normality assumption is satisfied) or Wilcoxon's signed-rank test (if normality assumption is not satisfied) will be performed depending on whether the assumption of normality is satisfied. To test the difference between the study groups and the control group (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group) for the changes from the baseline, the two-sample *t*-test (if normality assumption is satisfied) or Wilcoxon's rank-sum test (if normality assumption is not satisfied) will be performed depending on whether the assumption of normality is satisfied.

11.2.10.4. Electrocardiogram

For electrocardiography, the frequency and percentage by treatment group will be presented using the shift table for the changes in "normal or clinically insignificant abnormal" / "clinically significant abnormal" before and after administration. In addition, the intragroup comparison will use McNemar's test, while the intergroup comparison (GV1001 0.56 mg/day vs. control group, GV1001 1.12 mg/day vs. control group) will use Pearson's chi-square test or Fisher's test to perform analysis.

11.2.11. Handling Data of Dropout Subjects

The handling of data of dropout subjects out will be performed according to 11.2.2 Method of Handling Missing Data.

11.3. Analysis Period

No interim analysis will be performed in this clinical study, and the final analysis will be performed to prepare the clinical study report after the final visits of all subjects are completed.

11.4. Rationale for Setting Number of Subjects

This is a Phase 2a exploratory clinical study conducted for the purposes of collecting initial safety and efficacy information on the investigational product GV1001 in patients with progressive supranuclear palsy as well as providing the basis for design, evaluation items, and evaluation methods for subsequent clinical studies. Since this is a study to estimate the clinically significant effect size to demonstrate the efficacy of this investigational product, the number of subjects was not calculated based on statistical considerations. The minimum number of subjects required in a pilot study is 12 subjects[21] and approximately 30 subjects can be considered according to the rule of thumb[22, 23]. Therefore, by combining these, it is intended to set 20 subjects per group, and a total of 75 subjects with 25 subjects per group will be enrolled considering a dropout rate of 20%.

12. Data Management

12.1. Data Collection/Access

Source documents refer to the patient records of the physician in charge, which are kept at the study site. Most source documents are charts of the hospital or physician in charge, and in these cases, all information collected and recorded in the patient's case report form must be consistent with the relevant charts. This clinical study will collect data by using electronic case report forms, and only authorized individuals will be allowed to access and correct the data. The investigator shall ensure that the sponsor, the clinical research associate (hereinafter referred to as the "monitor"), the auditor, or the inspector has direct access to relevant data such as basic clinical study documents including electronic documents.

12.2. Data Protection/Storage

The investigator shall store various data and records related to the conduct of the clinical study in a secure location and maintain their security, and shall retain them for 3 years from the product approval date of the investigational product. After completion of the clinical study report, the documents related to the clinical study shall be transferred to the person in charge of storage, and the sponsor shall be informed in advance if the investigator intends to destroy the records related to the clinical study or move them to another location. However, the storage period may be extended if instructed by the Minister of Food and Drug Safety or if deemed necessary by the sponsor. The sponsor shall inform the investigator and the director of the study site regarding the need for data storage as well as the data storage duration in writing, and if the sponsor determines that the data no longer need to be stored, the sponsor shall inform the principal investigator and the director of the study site of this fact in writing.

13. Ethical Considerations and Administrative Procedures

13.1. Relevant Laws and Regulations

This clinical study will be conducted in accordance with all international and domestic laws and regulations, including the Declaration of Helsinki (1964) and the Korean Good Clinical Practice (KGCP), approval of the clinical study plan by the Ministry of Food and Drug Safety, approval from the IRB of the principal investigator's affiliated study site, and the standard operating procedures (SOPs) of the contract research organization, CMIC Korea Co., Ltd.

13.2. Subject's Consent

A written informed consent form shall be obtained from each subject prior to participation in the clinical study or prior to performing certain unconventional procedures that pose risks to the subject. The subject's informed consent form will be submitted to the relevant IRB by the principal investigator for review and approval prior to the start of the study.

Prior to the recruitment and enrollment of subjects, the clinical study details as well as the effects and adverse events of the investigational product and all information on safety will be described to the subject, and then the clinical study will be initiated after obtaining the subject's informed consent form which confirms that the subject will voluntarily participate in this clinical study.

If the subject or the legally authorized representative is unable to read the informed consent form, subject information sheet, and other documented information, an impartial witness will attend the entire process of obtaining consent. In this case, after reading and explaining all documented information to the subject or legally authorized representative, the subject or legally authorized representative shall be allowed to provide verbal consent for the subject's participation in the clinical study, and if possible, the subject shall be allowed to sign and date the informed consent form in his/her own handwriting. In addition, prior to the impartial witness signing the informed consent form, he/she shall also confirm that the documented information was accurately explained to the subject or legally authorized representative, and that the subject or legally authorized representative understood the relevant facts and that process of obtaining consent was conducted according to their own free will.

The original informed consent form will be signed by the patient and the principal investigator (or his/her delegatee), and the principal investigator or the investigator's delegatee will provide a copy of the original signed informed consent form to the subject. The original informed consent form will be retained by the investigator at the study site.

13.3. Indemnification Policy for Injured Subjects

In the case that an adverse event is caused by the investigational product or an injury occurs in the course of a corrective treatment of an adverse event, the principal investigator will indemnify the subject in accordance with the subject indemnification policy for the injury directly caused by the investigational product.

13.4. Criteria for Medical Care and Treatment of Subjects after Completion of Study Participation or Dropping Out

The investigator shall ensure that other appropriate treatments can be received by the subjects who have been dropped out from the clinical study or who do not show response, and shall ensure that subjects who have completed the clinical study also receive appropriate alternative treatments if it is determined that continuous treatment is required.

13.5. Ethics Compliance and Protection Measures for Subject Safety

This clinical study will be conducted scientifically and ethically in accordance with the Korean Good Clinical Practice and the laws and regulations relevant to clinical studies. In addition, this clinical study will be conducted in accordance with the Declaration of Helsinki to respect the dignity, rights, and interests of human beings, and to avoid placing disadvantages on the subjects.

• Study site

The director of the study site shall ensure that clinical laboratories, facilities, and specialized personnel necessary to conduct the clinical study are in place, and shall ensure that the clinical study can be properly conducted by allowing necessary actions to be taken in the case of an emergency.

• Institutional Review Board (IRB)

The IRB shall be organized according to domestic regulations/practices, and shall protect the rights, safety, and well-being of the subjects, and carefully review the validity of the reason in the case that vulnerable subjects participate in the clinical study. In performing its duties, the IRB shall take necessary actions such as issuing an order of discontinuation to the principal investigator for a part or for the entire clinical study if the subjects' consent for participation is not appropriately obtained, or the clinical study is not conducted in accordance with the protocol, or if serious adverse events and adverse drug reactions are shown. The IRB shall evaluate/approve this protocol in accordance with the Korean Good Clinical Practice, and shall regularly evaluate whether the clinical study is conducted in accordance with the protocol.

• Investigator

The word "investigator" refers to the principal investigator, sub-investigator, and coordinating investigator. Prior to enrolling subjects in the clinical study, the investigator shall check the health status of each subject to confirm whether he/she can participate in the clinical study. In addition, the investigator shall be sufficiently familiar with the study drug and make every effort to ensure the safety of the subjects. If medical treatment is needed for the subject's intercurrent disease which the investigator has become aware of, this shall be informed to the subject. The investigator shall accurately analyze and comprehend the clinical study plan, and actively respond to the issues of the subject.

• Sponsor

This refers to the individual, company, institution, and organization with responsibilities related to the planning, management, finances, etc., of the clinical study. It shall ensure that the subject of the clinical study, test methods, and case report forms and their details are managed in accordance with the procedures in the clinical study protocol. The sponsor's audit plan and procedures shall be determined based on the importance of the clinical study, the number of subjects, the type and complexity of the clinical study, the level of potential risks to the subjects, and the issues in conducting the clinical study that have already been identified.

The subjects' information and medical records obtained in this clinical study will be shared only with the principal investigator, the investigator's delegatee, and CRO, and may only be provided upon request by the jurisdictional departments such as the IRB and the Ministry of Food and Drug Safety.
In the case that an adverse event due to the clinical study has occurred, appropriate medical measures will be taken until the subject recovers, and the subject will be indemnified for the injury caused by the investigational product in accordance with the indemnification policy for injured subjects.

13.5.1. Approval and Amendment of Clinical Study Plan

The clinical study plan shall be submitted to the Ministry of Food and Drug Safety in accordance with Article 24 Paragraph 1 of the "Regulations on the Safety of Drugs, etc.," and the decision of the Ministry of Food and Drug Safety and the IRB regarding the conduct of the clinical study will be delivered to the investigator and the sponsor in writing before the start of the clinical study. The protocol, informed consent form, advertisements used for subject recruitment, and other written information provided to the subject (or the subject's legally authorized representative) regarding this study shall be approved by the Ministry of Food and Drug Safety and/or the IRB, and the documents shall be retained by the investigator and the sponsor.
The principal investigator or the investigator's delegate is responsible for undergoing a continuation review of the clinical study at intervals within 1 year or as otherwise specified by the IRB.

The principal investigator and the sponsor shall submit reports to the Ministry of Food and Drug Safety and/or the IRB on the progress of the clinical study, serious adverse events, life-threatening issues or deaths, and inform the Ministry of Food and Drug Safety and the IRB of this at the end of the clinical study.

Any amendments to the protocol shall be made through a consultation between the investigator and the sponsor, and any changes to the protocol shall be approved by the Ministry of Food and Drug Safety and the IRB prior to implementation. However, if the details of the protocol that do not significantly affect the safety of the subjects or the reliability of the study results are to be amended in accordance with Article 10 Paragraph 2 of the "Regulations on Approval for Investigational New Drug Application," it may be done after obtaining an approval from the IRB without a separate approval from the Ministry of Food and Drug Safety. Administrative changes do not generally require an IRB approval, but the IRB shall be informed of the relevant information.
Changes related to the safety of the subjects may be implemented without the approval of the Ministry of Food and Drug Safety and the IRB if a subject's sudden injury needs to be eliminated, and in such cases, the investigator shall submit reports to the Ministry of Food and Drug Safety and the IRB within a specified period after treatment and obtain approval.

13.5.2. Protocol Violations

The principal investigator or sub-investigator may violate the protocol or implement changes without a prior IRB approval in order to eliminate immediate risks posed to the subjects. After such occurrences, the committed violations or implemented changes, their reasons, and all proposed amendments to the protocol shall be submitted to the IRB for review and approval as soon as possible, and if necessary, they shall be also submitted to the regulatory authorities.
The principal investigator will report to the IRB any major protocol violations and violations deemed to be significant that affect the safety and integrity of this study.

13.6. Disclosure of Results

The sponsor shall prepare a report and inform the investigator of the results of the clinical study once the data from all study sites have been fully analyzed.

All data and results obtained from this clinical study are the property of the sponsor, and the sponsor has the right to publish the results of this clinical study at any time. The investigator shall not publish, present, or disclose any information related to the results of this study without a prior written consent of the sponsor, and shall also ensure that the sub-investigator complies with these conditions. To ensure that only accurate and validated data are used, the investigator shall provide the sponsor all draft publications or presentation manuscripts that were made prior to publication or presentation to discuss the materials with the sponsor, and the presentation shall be put on hold until a written approval is obtained.

For multicenter clinical studies, the investigator shall agree to not present the results of his/her affiliated study site or of some study sites prior to the presentation of the results collected from all of the study sites. However, exceptions are made when it is officially recognized by principal investigators of all study sites and the sponsor.

13.7. Confidentiality of Patient Records

All clinical study results and documents will be considered confidential. The investigator, the contract research organization, and the clinical research associate of the clinical study sponsor shall not disclose any information related to the clinical study without a signed approval of the clinical study sponsor. Records that can identify the subjects will be kept confidential, and all documents related to the clinical study, such as case report forms, will be recorded and classified with identification codes rather than the names of the subjects. Even when the results of the clinical study are published, the identities of the subjects shall be kept confidential.

13.8. Quality Control and Reliability Assurance

13.8.1. Monitoring of Clinical Study

Monitoring will be performed to protect the rights and well-being of the subjects, to confirm the accuracy, integrity, and verifiability of data through comparisons of reported clinical study data with source documents, and to confirm that the clinical study is being conducted in accordance with the approved protocol and Article 30 of the "Regulations on the Safety of Drugs, etc." and Appendix 4. Korean Good Clinical Practice.
A monitor designated by the sponsor will conduct monitoring of the clinical study, evaluate the progress of the clinical study, and check whether the investigator is fulfilling his/her obligations according to the protocol and regulations through regular visits to the study site and telephone calls. At visits to the study site, the monitor will check the original subject records, case report forms, drug management records, and storage of clinical study-related data. If any discrepancies or issues are found in the clinical study records, they will be discussed with the investigator.

13.8.2. Audit and Inspection

To ensure the safety of the subjects in this clinical study and to obtain accurate, complete, and reliable data, the investigator shall keep the clinical test results, clinical records, and the subjects' medical records as source documents. The principal investigators or sub-investigators and study sites participating in this study shall permit study-related monitoring, audits, IRB reviews, and inspections by regulatory authorities. The investigator shall allow direct access to the clinical study-related data upon request of the Ministry of Food and Drug Safety and the Institutional Review Board.

13.9. Other Matters Necessary to Conduct Clinical Study Safely and Scientifically

Through a meeting of investigators prior to the start of the clinical study, violations in the clinical study will be minimized by reviewing relevant documents such as the protocol and gathering the opinions of the investigators. In addition, an interim investigator meeting may be held if the sponsor or investigators determine that it is necessary to control the study sites and resolve violations, etc.

13.9.1. Matters Necessary to Initiate Clinical Study

The following are required prior to delivering the investigational product to the study site and prior to initiating the clinical study.

1) A copy of the approved protocol, and (if necessary) a copy of the approved protocol amendment
2) Career history of the principal investigator and sub-investigator
3) A written notification of approval of the clinical study plan by the Ministry of Food and Drug Safety and IRB
4) Copies of the subject information sheet and informed consent form
5) Normal ranges for clinical laboratory results
6) Other documents required by the government

Subjects shall not be enrolled prior to a formal meeting between the investigator and the sponsor for initiating the clinical study, and the meeting shall include conducting reviews on the protocol and case report forms.

13.9.2. Investigator's Obligations

The investigator is obligated to conduct the clinical study in accordance with the protocol, and has the responsibility of obtaining written informed consent from the subjects, or if necessary, the subjects' legally authorized representatives and guardians prior to performing any processes in accordance with the protocol.

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[Protocol Approval Letter]

Title: 진행성 핵상 마비 환자를 대상으로 GV1001 0.56 또는 1.12 mg/day 피하 투여 시 질환의 중증도 개선 효과와 안전성을 탐색하기 위한 다기관, 무작위배정, 이중 눈가림, 위약 대조, 평행 설계, 전향적, 제2a상 임상시험

A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel design, Prospective, Phase IIa Exploratory Clinical Trial to evaluate the efficacy and safety of Subcutaneous Administration of GV1001 0.56 or 1.12 mg/day in Patients with Progressive Supranuclear Palsy

Protocol No.: GV1001-PSP-CL2-011 **Version (Date):** 5.1 (15 Mar 2024)

I have read and reviewed this protocol, and I understand and agree that this protocol contains all the information necessary to conduct the clinical study. I will make reasonable efforts to complete this clinical study within the planned schedule. I will conduct this clinical study in accordance with the Declaration of Helsinki, ICH Good Clinical Practice (GCP), and all applicable regulations of relevant countries.

Sponsor

성명
Printed Name _____

서명
Signature _____

날짜(DD/MMM/YYYY)
Date _____

[Protocol Approval Letter]

Title: 진행성 핵상 마비 환자를 대상으로 GV1001 0.56 또는 1.12 mg/day 피하 투여 시 질환의 중증도 개선 효과와 안전성을 탐색하기 위한 다기관, 무작위배정, 이중 눈가림, 위약 대조, 평행 설계, 전향적, 제2a상 임상시험

A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel design, Prospective, Phase IIa Exploratory Clinical Trial to evaluate the efficacy and safety of Subcutaneous Administration of GV1001 0.56 or 1.12 mg/day in Patients with Progressive Supranuclear Palsy

Protocol No.: GV1001-PSP-CL2-011 **Version (Date):** 5.1 (15 Mar 2024)

I have read and reviewed this protocol, and I understand and agree that this protocol contains all the information necessary to conduct the clinical study. I will make reasonable efforts to complete this clinical study within the planned schedule. I will conduct this clinical study in accordance with the Declaration of Helsinki, ICH Good Clinical Practice (GCP), and all applicable regulations of relevant countries.

Principal Investigator

성명
Printed Name _____

서명
Signature _____

날짜(DD/MMM/YYYY)
Date _____