Statistical analysis plan
Clinical trial protocol

Efficacy and Safety of Personalized Digital Therapy Based on Visual Perceptual Learning for Visual Field Defects in Stroke

A Prospective Multicenter Randomized Controlled Trial

Investigational Device: VIVID Brain

Protocol No.: NNS-VB-02

Sponsor: (C) Nunaps

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General Information

Summary of clinical trial protocol

Name	Efficacy and Safety of Personalized Digital Therapy Based on Visual Perceptual Learning for Visual Field Defects in Stroke: A Prospective Multicenter Randomized Controlled Trial
Sponsor	(C) Nunaps Room 1, 11th floor, Asan Life Science Research Institute Convergence Research Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul
Principal investigators	• Kim Kyeong-moon, Department of Neurology, Samsung Seoul Hospital • Beomjun Kim, Department of Neurology, Asan Medical Center, Seoul • Moon-gu Han, Department of Neurology, Seoul National University Bundang Hospital • Hanyoung Kim, Department of Neurology, Konkuk University Hospital • Park Gwang-yeol, Department of Neurology, Chung-Ang University Hospital • Koo Ja-seong, Department of Neurology, Seoul St. Mary's Hospital, Catholic University of Korea • Kyeong-Ho Yoo, Department of Neurology, Hallym University Sacred Heart Hospital • Hong Geun-sik, Department of Neurology, Inje University Ilsan Paik Hospital • Jo Ah-hyun, Department of Neurology, Yeouido St. Mary's Hospital • Jinman Jeong, Department of Neurology, Korea University Ansan Hospital • Ji-Hyeon Kwon, Department of Neurology, Ulsan University Hospital • Jaeguk Kim, Department of Neurology, Daejeon Eulji University Hospital
Centers	

Test institution	Address
Samsung Seoul Hospital	81 Ilwon-ro, Gangnam-gu, Seoul
Seoul Asan Medical Center	88 Olympic-ro 43-gil, Songpa-gu, Seoul
Seoul National University Bundang Hospital	82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do
Konkuk University Hospital	120-1 Neungdong-ro, Gwangjin-gu, Seoul
Chung-Ang University Hospital	102 Heukseok-ro, Dongjak-gu, Seoul
Catholic University Seoul St. Mary's Hospital	222 Banpo-daero, Seocho-gu, Seoul
Hallym University Sacred Heart Hospital	22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do
Inje University Ilsan Paik Hospital	170 Juhwa-ro, Ilsanseo-gu, Goyang-si, Gyeonggi-do
Catholic University Yeouido St. Mary's Hospital	10 63-ro, Yeongdeungpo-gu, Seoul
Korea University Ansan Hospital	123 Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do

	Ulsan University Hospital: 877 Bangeojin Ring Road, Dong-gu, Ulsan Metropolitan City Daejeon Eulji University Hospital: 95 Dunsanseo-ro, Seo-gu, Daejeon
Medical device	Product name: VIVID Brain (Model name: NNS-VB)
Time period	36 months from the date of approval of the clinical trial plan by the Ministry of Food and Drug Safety
Patients	Patients with visual field defect due to brain disease
Purpose	To evaluate the safety and effectiveness of visual perception learning training, provided by VIVID Brain, in patients with visual field defects due to brain disease as compared to the no-training.
Design	Multi center, Randomized, Single-blind (Evaluator), Prospective Confirmatory study
Drugs / Treatment not allowed	1) Do not add any eye drops that may affect this clinical trial, such as mydriatics, 6 hours before conducting this clinical trial. 2) Neuroactive agents (methylphenidate, modafinil, amphetamine) should not be used concurrently during the period of this clinical trial.
Inclusion criteria	1) Men and women over 19 years of age 2) Those who have had brain disease related to visual impairment for more than 3 months 3) Those who have been confirmed to have brain disease in the visual pathway such as the occipital lobe, parietal lobe, and temporal lobe through MRI or CT 4) Those who have no difficulty using VR devices 5) Those who can use the application using a smartphone 6) Those who voluntarily signed the consent form
Exclusion criteria	1) Patients with complete hemianopia 2) Those with epilepsy, photosensitivity, or Parkinson's disease 3) Patients with bilateral visual field defect 4) Those with symptoms of hemispatial neglect 5) People suffering from eye diseases that interfere with the performance of this clinical trial, such as ptosis, corneal opacity, diabetic retinopathy, glaucoma, and macular degeneration that affect vision. 6) Those who cannot stop taking neuroactive drugs (methylphenidate, modafinil, amphetamine) 7) Those considering cerebrovascular stent implantation or carotid endarterectomy 8) Those who have undergone eye surgery or laser surgery (excluding cataracts) within 3 months of conducting this clinical trial 9) Pregnant and lactating women 10) Persons participating in intervention clinical trials other than this clinical trial 11) Other people judged by the investigator to be unsuitable for this clinical trial
Criteria for termination/drop-out	**Criteria for termination** 1) When it is deemed difficult to continue clinical trials 2) If you wish to stop the clinical trial for reasons such as the safety of the clinical trial medical device. 3) If the subject is discontinued due to an adverse event/serious adverse event/medical device adverse reaction that makes it difficult to proceed with the clinical trial. 4) In other cases where the test manager determines that the test should be

	stopped **Criteria for drop-out** 1) Then the subject or legal representative voluntarily withdraws consent to stop the clinical trial 2) If an adverse event (dizziness, etc.) appears during follow-up that makes it difficult to continue conducting the clinical trial. 3) In case of violation of selection/exclusion criteria 4) When surgery, drugs, or other medical devices that may affect safety and effectiveness evaluation are used concurrently 5) If a serious adverse event occurs and the investigator determines that participation in the clinical trial is not appropriate 6) In the test group only, the test device was never applied during the clinical trial period. 7) When primary or secondary efficacy endpoints are not observed after randomization 8) Those who do not meet the reliability standards of the Humphrey visual field test 9) When the principal investigator determines that he/she is not appropriate as a subject (if the subject does not comply with the investigator's instructions, if the subject's condition changes and it is determined that participation in the clinical trial is no longer possible in terms of safety or ethics, etc.)
Efficacy outcome measures	**Primary endpoint:** Improved visual field area at 12 weeks compared to baseline in the entire visual field [(a)] **Secondary endpoint:** 1) Improved defective visual area at 12 weeks compared to baseline [(a)] 2) Changed visual field score at 12 weeks compared to baseline in the whole field [(b)] 3) Changed visual field score at 12 weeks compared to baseline in the defective field [(c)] [(a)] A blinded evaluator assesses the area where luminance detection sensitivity has improved by more than 6dB (Humphrey Visual Field Testing 30-2; SITA-Fast) [(b)] A blinded evaluator assesses changes in Perimetric Mean Deviation (Humphrey Visual Field Testing 30-2; SITA-Fast) [(c)] A blinded evaluator assesses average changes in Total Deviation (Humphrey Visual Field Testing 30-2; SITA-Fast)
Safety outcome measures	All adverse events occurring from the time of screening to 12 weeks (Visit 3) are included in the safety evaluation, and all adverse events are recorded in the case record and evaluated for abnormalities. **Adverse events:** Adverse events are recorded as clinically significant abnormal symptoms or signs at the following time points. In addition, all adverse events that occur are recorded for each subject, including causality and severity, according to the items presented in this clinical trial protocol. 1) Abnormal symptoms and signs from the time of screening until immediately before application of the clinical trial medical device are evaluated and recorded through physical examination. 2) While applying the medical device, check and record any adverse events that

Methods

occur after applying the medical device.

Vital signs & Physical examination:

- Vital signs: sitting blood pressure, pulse, temperature
- Physical examination: Check for unusual symptoms and signs

The multi center, randomized, single-blind (evaluator), prospective confirmatory study is to evaluate the safety and effectiveness of visual perception learning training, provided by VIVID Brain, in patients with visual field defects due to brain diseases and to confirm improvement in visual field defect using Humphrey visual field test (HVF 30-2, SITA-Fast).The participants include patients with visual field defect due to brain disease. The participants who agreed to participate were screened for eligibility.

- **Screening test**: Recruit subjects who meet the inclusion/exclusion criteria.
- **Randomization**: Subjects who meet the inclusion/exclusion criteria are randomly assigned to the control group and test group in a 1:1 ratio according to the randomization code stratified by clinical trial participating institution.
- **Single blinding of the evaluator**: A blinded independent evaluator is selected to evaluate the efficacy endpoints.

- **Visual perceptual learning-based training and monitoring using VIVID Brain**
  - Test group: After being thoroughly familiar with the usage and precautions of medical devices, a total of 60 training sessions will be conducted at home 5 times a week (6 blocks per session, within 30 minutes) for 12 weeks from baseline (Visit 2) to the 12th week of study participation (Visit 3).
  - Control group: No training is provided for 12 weeks from baseline (Visit 2) until the 12th week of study participation (Visit 3). After completing the safety and efficacy evaluation at the 12th week (Visit 3), patients wishing to receive visual perception learning will be able to participate in the training at home from the 12th week (Visit 3) after accurately familiarizing with the usage and precautions of medical devices. Training can be conducted 5 times a week (6 blocks, approximately 30 minutes per session) for 12 weeks until the 24th week of participation (Visit 4), for a total of 60 training sessions.

Safety assessment

Safety outcomes will be collected between screening and week 12 (Visit 3). However, safety evaluations collected after 12 weeks (Visit 3) in the control group are not analyzed as safety outcome measures in this clinical trial.

Efficacy assessment

The blinded evaluator, not aware of the type of the training, will perform the Humphrey visual field test at baseline (Visit 2) and at 12 weeks of study participation. The collected Humphrey visual field tests are blindly provided to the evaluator as a test group and a control group, and the results for the efficacy endpoints are collected. The primary and secondary outcome measures do not include efficacy measures collected after 12 weeks (Visit 3) in the control group.

Study participants

	Training group	Control group	Total

	<table><tr><td>Target number of subjects</td><td>41</td><td>41</td><td>82</td></tr><tr><td>Number of subjects considering drop-out of 20%</td><td>52</td><td>52</td><td>104</td></tr></table> The primary efficacy endpoint of this clinical trial is the improved visual area at 12 weeks compared to baseline. Based on the previous findings on clinical trials for visual field defect improvement, the mean and standard deviation of the test group were estimated as 111.6 and 117.5, and the mean of the control group was estimated to be 37.2 (average 33.3% of the test group). Based on this, considering the power of 80%, the two-sided significance level of 5%, and the dropout rate of 20%, we aimed to enroll a total of 104 subjects (52 in each group), leading to a total of 82 participants (41 in each group) as the FA group specified in the clinical trial protocol.
Statistical analysis methods	**General principles:** The subjects of this clinical trial are largely divided into the Safety group, Intent-to-treat (ITT) group, Full Analysis (FA) group, and Per-Protocol (PP) group. All efficacy measures will be analyzed in the FA group as the main analysis. The efficacy measures will be analyzed in the PP group to confirm the robustness of this clinical trial. Safety measures will be analyzed for the Safety group. The FA group includes all subjects for whom the primary endpoint was measured after randomization. However, subjects who violate serious selection/exclusion criteria are excluded. The PP group includes the subjects who did not commit any major violations of the clinical trial plan in the FA group. The safety group includes all randomly assigned subjects, who will be analyzed according to the actual treatment group. A comprehensive Statistical Analysis Plan (SAP) will be created before data locking (DB lock) of the clinical trial. The SAP will include more technical and detailed explanations than the statistical analysis in this clinical trial plan. For the primary efficacy endpoint, statistical analysis will be conducted under a two-sided significance level of 5% in accordance with the basis used for sample size estimation. The statistical analysis for all other efficacy and safety endpoints will be conducted under a two-sided significance level of 5%. The validity using the Humphrey visual field test needs to be accurately evaluated. If the reliability standard of the visual field test (less than 20% for both fixation loss and false positives) is not met in the Humphrey visual field test during research participation, retesting is possible. If the reliability criteria are not still met after retesting, the validity evaluation is deemed impossible. In the case of the control group, safety and efficacy measures, collected after 12 weeks of study participation (Visit 3) will not be analyzed as the main efficacy measures of this clinical trial. Therefore, once the data for all subjects at 12 weeks (Visit 3) is collected, the first DB lock will be performed. Then, the data will be analyzed to prepare the final report of the clinical trial. After the first DB lock, once the data is collected after 12 weeks (Visit 3) of the control group, the second DB lock will be performed and the dataset will be not included in the analysis of the main endpoints of this clinical trial. **Primary efficacy endpoints:** The primary efficacy endpoint of this clinical trial includes improved visual area

improved at 12 weeks compared to baseline, which is a continuous variable. To compare between the test group and the control group, the distribution of the relevant variables will be tested. As long as the distribution of values does not significantly deviate from the normality assumption, Student's t-test will be used for the comparisons. If the normality assumption is not satisfied, the non-parametric Wilcoxon rank sum test will be used. If the statistical test result is significant under the two-sided significance level of 5% and the mean or median of the test group is greater than that of the control group, the test group will be judged to be superior to the control group

Secondary efficacy endpoints

All secondary efficacy measures in this clinical trial are continuous variables. As long as the distribution of the relevant measures does not significantly deviate from the normality assumption, the secondary efficacy measures will be compared between the test and control groups using Student's t-test. If the normality assumption is not satisfied, the non-parametric Wilcoxon rank sum test will be used for the between-group comparison.

For changes in visual field score for 12 weeks in the whole field and defective hemifield, analysis of covariance will be additionally performed by including the baseline value of the relevant variables as covariates.

Adverse events:

For the analysis of adverse events, adverse events (Treatment Emergent Adverse Events, TEAE) that occurred after application of clinical trial medical devices will be analyzed, and all adverse events will be listed. For all adverse events, the number and ratio of adverse events will be presented by SOC and PT. The 95% confidence interval is presented for subjects who experienced more than one adverse event. Pearson's chi-square test or Fisher's exact test will be performed to compare the between the test and control groups.

Vital signs and physical examination:

Vital signs such as systolic blood pressure, diastolic blood pressure, and pulse, as well as physical examination such as height and weight, will be presented using descriptive statistics such as mean, standard deviation, median, interquartile range, minimum and maximum values at each visit within each treatment group. Mixed effects model of repeated measures (MMRM) analysis will be used to evaluate changes in vital signs and physical examination during the clinical trial period. In the repeated measures mixed effects model (MMRM) analysis, the main effects of test group and visit, the test group-visit interaction will be included as fixed effects. An unstructured covariance matrix structure will be used.

Concomitant medications:

The summary statistics of concomitant medications for each group will be presented in steps 1 and 2 using the WHO ATC code for each subject.

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Schedule Summary of Clinical Trial

		Test group				Control group			
Schedule		**Screening[1)]**	**Baseline[1)]**	**Follow-up**		**Screening[1)]**	**Baseline[1)]**	**Follow-up**	**UV[8)]**
Visit		**V1**	**V2**	**Phone Screening[2)]**	**V3**	**V1**	**V2**	**V3**	
Visit Period		**-4w**	**0w**	**1w +7d**	**12w ±10d**	**-4w**	**0w**	**12w ±10d**	
Written consent		V				V			
Demographic information		V				V			
Medical history		V				V			
Vital Signs[3)]		V	V		V	V	V	V	
Physical Examination[4)]		V	V		V	V	V	V	
Humphrey visual field test[5)]			V		V		V	V	
Inclusion/exclusion criteria		V	V			V	V		
Randomization[6)]			V				V		
MEDICAL DEVICE	**Educate on usage of the medical device**		V					(V)[9)]	
	Reeducate on usage of the medical device			V					
	Reeducate								(V)
	Return				V				
	Compliance check[7)]				V				
Preceding/concomitant medications		V	V		V	V	V	V	
Adverse events			V		V		V	V	V

1) Screening and randomization may occur on the same day
2) Check whether retraining is needed on how to use medical devices for clinical trials through a non-face-to-face phone call.
3) Vital signs: sitting blood pressure, pulse, temperature
4) Physical examination: Check for unusual symptoms and signs
5) If the visual field test reliability criteria (fixation loss, false positives, and false negatives are all less than 20%) are not met, retesting is possible. In the case of baseline visual field testing, it can be replaced if there are test results within 2 weeks.
6) Randomization: Randomization is performed only on subjects who meet the selection/exclusion criteria.
7) Access VIVID Brain Web and check the number of training sessions through training records
8) Unscheduled Visit : Retraining on how to use (test group only) with additional visits when necessary due to adverse events, etc.

Abbreviations

ADE	Adverse device effect
AE	Adverse event
FA	Full Analysis
HVF	Humphrey Visual Field
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
KGCP	Korean Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events

1. Effectiveness evaluation criteria, evaluation method, and interpretation method (according to statistical analysis method)

1.1 General principles

Before the data locking of this clinical trial is completed, a comprehensive Statistical Analysis Plan (SAP) will be created and will include more technical and detailed explanations than the statistical analysis in this clinical trial plan. For the primary efficacy endpoints, statistical analysis will be conducted under a two-sided significance level of 5% in accordance with the evidence used to calculate the number of subjects, and statistical analysis for the secondary efficacy and safety endpoints will be conducted under a two-sided significance level of 5%.

If a subject drops out of an efficacy endpoint before the end of the clinical trial and a missing value occurs, the primary efficacy evaluation is conducted at the early termination visit, and the value of the primary efficacy evaluation in which the missing value occurred is replaced with the corresponding value for analysis. Missing value processing is applied only to the FA group, and other items are analyzed using data (available data set) that does not replace missing values.

In the case of the control group, the safety and efficacy evaluation values collected after 12 weeks of study participation (Visit 3) will not be considered as the outcome measures. We do not plan to analyze it as the main evaluation variable of the test. Therefore, once the data for all subjects at 12 weeks (Visit 3) is collected, the first DB lock is performed, the data is analyzed, and the final clinical trial result report is prepared. Once data is collected after 12 weeks (Visit3) in the control group after the first DB lock, the second DB lock will be performed, but will not be included in the analysis of the main endpoints of this clinical trial.

1.2 Target group for analysis

The validity evaluation targets for the data obtained from the subjects of this clinical trial are the intent-to-treat (ITT) population, the full analysis set (FAS) population, and the protocol-compliant analysis population. It is divided into (Per Protocol (PP) population), and the safety analysis target group (Safety population) is used for safety evaluation.

The definition of the ITT analysis target group is as follows: The ITT analysis target group includes all randomly assigned subjects. In other words, all subjects assigned to the treatment group according to random assignment are included, regardless of whether the medical device to which the subject was randomly assigned matches the medical device actually applied.

The definitions for the FAS analysis target group are as follows: Among the ITT analysis target group, these are all subjects for whom the primary endpoint was measured. However, subjects who violate serious selection/exclusion criteria are excluded.

When excluding subjects who violate significant selection/exclusion criteria from the analysis, the following conditions must be met to prevent bias.

1) Cases where inclusion/exclusion criteria are assessed prior to randomization
2) When the discovery of violations of appropriate selection criteria is made completely objectively.
3) When all clinical trial subjects are objectively and equally reviewed for violations of selection criteria under blinded conditions.
4) In case of excluding all clinical trial subjects found to have violated specific selection/exclusion criteria

The definition of the PP analysis target group is as follows: The following are considered major violations of the clinical trial plan. The PP analysis target group is the subjects who did not commit any violations of the major clinical trial plans below in the FAS analysis target group. The last of the major violations below, ‘Cases that can be considered other serious violations of the plan,’ is finalized before data locking.

Critical Protocol Violation

- Subjects who dropped out of clinical trials
- Violation of selection/exclusion criteria
- Randomization error
- Taking drugs contraindicated in combination and receiving treatment prohibited in combination
- Application of clinical trial medical devices before randomization
- Randomization performed prior to written consent
- Other cases that may be considered serious violations of the plan

The definition of the safety population is as follows: The safety analysis target group includes all randomly assigned subjects. Subjects are analyzed according to the treatment group they actually received.

The general characteristics of the subjects are summarized using the FAS analysis group.

All effectiveness analyzes are performed as the main analysis in the FAS analysis group, and analysis is also performed in the PP analysis group to confirm the robustness of this clinical trial. Safety evaluation variables such as adverse reactions are analyzed using the safety analysis target group.

1.3 Demographic survey and clinical history data

Categorical data will be summarized with frequencies and corresponding proportions for each group. For continuous data, descriptive statistics for each group are presented using the number of subjects, mean, standard deviation, median, interquartile range, minimum and maximum values. Descriptive analysis is used to summarize pre-treatment characteristics for each treatment group.

When comparing between two groups, in principle, Student's t-test is performed for continuous variables as long as they do not significantly deviate from the normality assumption, but if normality is not satisfied, the non-parametric Wilcoxon rank sum test is performed. At this time, the normality assumption is evaluated based on the histogram of each continuous variable. Chi-square test is performed for categorical variables, but when the number of data is not large and the assumptions required for the parametric test are not satisfied, Fisher’s exact test is performed.

Statistical analysis of baseline data is performed in an entirely exploratory manner. If there is a difference in baseline data between the two groups (based on $P<0.05$), additional analysis will be performed to determine how the imbalance in baseline data affects the primary efficacy evaluation variable, and covariance analysis will be used as a statistical analysis method. Analysis of Covariance will be used.

1.4 Analysis of primary efficacy evaluation variables

Descriptive statistics (mean, standard deviation, median, quartile) for the visual area improved by more than 6dB in the entire field of Humphrey visual field (HVF) compared to baseline as assessed by a blinded evaluator at 12 weeks compared to baseline for the test and control groups range, minimum value, maximum value). As long as the distribution of primary efficacy endpoint values does not significantly deviate from the normality assumption, they are compared using Student’s t-test. If the normality assumption is not satisfied, the non-parametric Wilcoxon rank sum test is used.

If the statistical test result is significant under the two-sided significance level of 5% and the mean or median of the test group is greater than that of the control group, the test group is judged to be superior to the control group.

In order to accurately evaluate validity, if the Humphrey visual field test at 12 weeks does not meet the reliability standards of the visual field test (fixation loss, false positives, and false negatives are all less than 20%), the test can be retested. If the reliability standards are not met even after the retest, the validity evaluation is deemed impossible. [16].

1.5 Analysis of secondary efficacy endpoints

1) **Visual area improved by more than 6 dB in impaired vision on the Humphrey visual field test (HVF) at week 12 compared to baseline as assessed by a blinded evaluator**

Descriptive statistics (mean, standard deviation, median, and interquartile range) for the test and control groups for the change in visual area that improved more than 6 dB in the impaired field of Humphrey visual field (HVF) assessed by a blinded evaluator at 12 weeks compared to baseline. , minimum and maximum values) are presented. As long as the distribution of the relevant variable values does not significantly deviate from the normality assumption, they are compared using Student's t-test. If the normality assumption is not satisfied, the non-parametric Wilcoxon rank sum test is used.

2) Change in visual field scores of impaired vision and total vision in the Humphrey visual field test (HVF) at week 12 compared to baseline assessed by a blinded evaluator

Descriptive statistics (average) for the test group and control group for the change in the impaired visual field (Total Deviation mean score) and the total visual field score (Perimetric Mean Deviation) of the Humphrey visual field test (HVF) evaluated by a blinded evaluator at 12 weeks compared to the baseline. , standard deviation, median, interquartile range, minimum, and maximum values) and compare using Student's t-test as long as the distribution of the corresponding variable values does not significantly deviate from the assumption of normality. If the normality assumption is not satisfied, the non-parametric Wilcoxon rank sum test is used. Additionally, the statistical significance of differences within each group is tested using paired t-test or Wilcoxon signed rank test. Additionally, analysis of covariance is performed by correcting the baseline value of the variable.

*** Measurement and evaluation methods**

In order to accurately evaluate validity, if the Humphrey visual field test at 12 weeks does not meet the reliability standards of the visual field test (fixation loss, false positives, and false negatives are all less than 20%), the test can be retested. If the reliability standards are not met even after the retest, the validity evaluation is deemed impossible. [16].

2. Safety evaluation criteria, evaluation methods, and reporting methods, including side effects

2.1 Safety endpoints

All adverse events, including dizziness, that occurred during this clinical trial are included in the safety evaluation, and safety is evaluated through vital signs and physical examinations measured during the clinical trial. All adverse events are recorded in the case record and evaluated for abnormalities. However, safety evaluations collected after 12 weeks (Visit3) in the control group are not analyzed as safety evaluation variables in this clinical trial.

2.1.1 Adverse events

In this clinical trial, adverse events are 1) adverse events prior to application of the clinical trial test device (abnormal symptoms and signs appearing in medical history and physical examination) and 2) adverse events that occurred after application of the clinical trial test device (Treatment Emergent Adverse Events, TEAE), and adverse events that occurred after application of the test device for clinical trials are [1] adverse events that occurred for the first time after application of the test device for clinical trials, and [2] abnormal symptoms and signs that occurred before application of the test device for clinical trials, which occurred after application of the test device for clinical trials. It is defined as an adverse event when the severity worsens.

In the adverse event analysis, adverse events (TEAEs) that occurred after applying the test device for clinical trials are analyzed, and all adverse events are presented as a listing. All adverse

events that occur are standardized into SOC (System Organ Class) and PT (Preferred Term) using the latest version of MedDRA (Medical Dictionary for Regulatory Activities). An adverse event (TEAE) is considered as one case if the same adverse event occurs multiple times in one person based on SOC and PT, and if the severity of the same adverse event is different, it is treated as the maximum severity. do. In cases where the causal relationship for the same adverse event (TEAE) in one person is different, it is handled in a direction that is more related to the test device for clinical trials.
For all adverse events, the number and ratio of adverse events are presented by SOC and PT, and a 95% confidence interval is presented for subjects who experienced more than one adverse event.

Abnormalities that are clinically significant at the time below are recorded as adverse events, and the occurrence area is classified into test device application area and non-application area and recorded. In addition, all adverse events that occur are recorded for each subject, including causality and severity, according to the items presented in this clinical trial protocol.

1) Abnormal symptoms and signs from the time of screening until immediately before application of the clinical trial medical device are evaluated and recorded through medical history and physical examination.
2) Evaluation immediately after application of the medical device: Check and record local adverse events (dizziness, vomiting, etc.) at the application site that occur 30 minutes after application of the medical device for clinical trials.
3) Adverse events (TEAEs) that occurred from the time of final application of the clinical trial medical device until the end of the clinical trial are recorded.

2.1.2 Vital signs and physical examination

1) Vital signs: sitting systolic/diastolic blood pressure, pulse, temperature
2) Physical examination: Check for unusual symptoms and signs

2.1.3 Concomitant medication

Each subject is described, and summary statistics of concomitant medications for each group are presented in steps 1 and 2 using the WHO ATC code.

2.2 Safety evaluation criteria, evaluation and reporting methods

2.2.1 Adverse Event

The number and percentage of subjects are described by dividing each test group into the severity, severity, relationship with the test device, measures, and results of the adverse reaction. All adverse reactions that occur are classified and presented by body organ using MedDRA's preferred term (PT). A 95% confidence interval is presented for the number of cases of adverse reactions and the difference between groups in subjects who experienced one or more adverse reactions, and Pearson’s chi-square test or Fisher’s exact test is performed for comparison between test groups.If a subject dies during the clinical trial, relevant information will be provided in the data list and description of serious adverse events.

2.2.2 Vital signs and physical examination

Vital signs such as systolic blood pressure, diastolic blood pressure, and pulse, as well as physical examination such as height and weight, will present descriptive statistics such as mean, standard deviation, median, interquartile range, minimum and maximum values at each visit within each treatment group. Mixed effects model of repeated measures (MMRM) analysis is used to evaluate changes in vital signs and physical examination during the clinical trial period. In the repeated measures mixed effects model (MMRM) analysis, the main effects of test group and visit, the test group-visit interaction, etc. will be included as fixed effects, and an unstructured covariance matrix structure will be used.

2.3 Definition of safety-related terms

2.3.1 Adverse Event, AE

An adverse event refers to an undesirable and unintended sign, symptom, or disease that occurs in a subject during a clinical trial, and does not necessarily have a causal relationship with the medical device used in the clinical trial.

2.3.2 Adverse Device Effect, ADE

Adverse medical device reactions refer to all harmful and unintended reactions that occur due to a medical device for clinical trials and where the causal relationship with the medical device for clinical trials cannot be denied.

2.3.3 Serious AE/ADE

Serious adverse events/adverse medical device reactions refer to adverse events or adverse medical device reactions occurring due to medical devices used in clinical trials that fall under any of the following items.

1) When it causes death or poses a risk to life
2) When there is a need to be hospitalized or to extend the hospitalization period
3) If it causes persistent or significant disability or functional decline
4) If it causes congenital deformities or abnormalities

If the subject visits the emergency room and the treatment time exceeds 24 hours, the criteria for hospitalization are considered to have been met. If hospitalization is scheduled before the first application of the clinical trial medical device or is due to a pre-existing disease, it is an adverse event or serious adverse event. is not considered However, if hospitalization is unplanned or is the result of an adverse event, it is considered a serious adverse event.

Even if it is not a situation listed above, if a situation occurs that is medically considered to have a significant impact on the subject's well-being and health, it will be determined whether it will be considered a serious adverse event/adverse medical device reaction based on the medical judgment of the doctor in charge and related experts. Decide whether or not to do so and take appropriate action accordingly.

2.3.4 Unexpected ADE

An unexpected medical device adverse reaction means a difference in the pattern or degree of harm of a medical device adverse reaction in light of information related to the medical device for clinical trials (clinical investigator data sheet, attached documents of the medical device, etc.), and this must be promptly reported. is needed. Among serious medical device adverse reactions that have already been reported and known, additional significant information regarding their specificity or severity can be viewed as unexpected. For example, events that are more unusual or more serious than those recorded in the investigator data sheet are considered unexpected. Examples include: (1) acute renal failure is known to be a medical device adverse reaction, there is a new report of interstitial nephritis, and (2) cases where infection is reported after the first report of breakthrough hepatitis but before it is applied to the relevant document.

2.4 Recording and reporting procedures for adverse events

Undesirable and unintended signs, symptoms, and diseases that occur after randomization until the last visit are recorded as adverse events. Signs, symptoms, or diseases that appeared before application of the medical device will be considered adverse events only if they worsen after application of the medical device.

2.4.1 Records of adverse events

For all adverse events that occur immediately after application of the clinical trial medical device, the investigator records information in the case record using the guidelines and definitions described below when reporting the next adverse event.

1) Characteristics of adverse events: It is preferred to describe a comprehensive diagnosis or syndrome rather than individual symptoms/signs. Investigators must report adverse events using standard medical terminology. CRF and supporting document data must be consistent.
2) Date of onset (start date): Start date of adverse event, test date reported as abnormal for clinically significant test results
3) Severity: If an adverse event occurs, it must be reported according to the following severity evaluation criteria.

i. Mild: When it does not interfere with the subject's normal daily life (function), causes minimal discomfort, and is easily tolerated by the subject.
ii. Moderate: Cases that cause discomfort that significantly impairs the subject's normal daily life (function)
iii. Severe: When it makes the subject's normal daily life (function) impossible.

3) Record of actions regarding medical devices for clinical trials: Due to the occurrence of adverse events, actions related to the application of medical devices for clinical trials are recorded in the case record according to the following classifications

i. Suspension of application: When the subject chooses to discontinue application of the experimental medical device or the investigator determines that discontinuation of application of the experimental medical device is the best measure considering the subject's safety, and the application of the experimental medical device is discontinued due to this adverse event
ii. Reduction (reduction in application frequency): When the application of the investigational medical device is reduced due to this adverse event.
iii. Increased dose (increased application frequency): When the application of the investigational medical device is increased due to this adverse event
iv. No change: When the application of the investigational medical device remains the same despite the presence of adverse events
v. Unknown: When it is unknown what measures were taken due to the occurrence of an adverse event.
vi. Not applicable: In case of adverse events that occur when the investigational medical device is not applied (before and after the treatment period or in the case of single-dose clinical trials)

4) Other measures taken: Select from the following items regarding treatment for adverse events, etc. and record them in the case record.
i. None: No other action was taken for this adverse event.
ii. Drug application: For this adverse event, a specific drug (prescription or non-prescription drug) was applied or the existing drug dose was changed.
iii. Hospitalization or Extended Hospitalization: This adverse event resulted in the subject being hospitalized or having an extended hospital stay.
iv. Therapeutic or Diagnostic Procedures: Subject used other therapeutic measures or underwent diagnostic procedures due to this adverse event (e.g., additional laboratory tests, x-rays, etc.).
v. etc

5) Disappearance date (end date): Date of disappearance of adverse event. If an adverse event consists of several signs/symptoms (syndrome), the duration of the adverse event is determined by the sign/symptom with the longest duration.

6) Results: Changes in adverse events are judged based on the following criteria.

i. Recovered: The adverse event no longer exists. – Complete extinction
ii. Recovering: When the patient's condition is improving but symptoms still remain.
iii. Recovered, but aftereffects remain: The adverse event has recovered, but residual effects still remain.
iv. No recovery: When the patient's condition does not recover and there is no change in symptoms (e.g., when atrial fibrillation becomes chronic)
v. Death: This adverse event caused or directly caused the subject's death.
vi. unable to decide

7) Assessment of causal relationship between adverse events and medical devices:
When an adverse event occurs, the relationship with the medical device for clinical trials is assessed by the investigator in accordance with the evaluation criteria in Article 7, Review and Evaluation of Safety Information, Paragraph 2 [Appendix 2] of the Regulations on Management of Safety Information, including Side Effects of Medical Devices. Describe the tester's opinion

Definitely related	The relationship between the occurrence of an adverse event and the use of the medical device is reasonable, it is most likely explained by the use of the medical device rather than any other reason, the symptoms of the adverse event occurring when the medical device is discontinued disappear, and the reuse (reusable) is possible. (only carried out in cases where adverse event symptoms appear). Additionally, if the adverse event that occurred is consistent with information already known about the relevant medical device or medical devices of the same series.
Probably related	There is evidence of use of the medical device, the temporal sequence of use of the medical device and occurrence of the adverse event is reasonable, it is more plausibly explained by the use of the medical device than other causes, and it occurred due to discontinuation of use of the medical device. When the adverse event symptoms disappear
Possibly related	There is evidence of use of the medical device, the temporal sequence of use of the medical device and occurrence of the adverse event is reasonable, and it is judged to be attributable to the use of the medical device to the same extent as other possible causes, and the medical device If the symptoms of an adverse event that occurred due to discontinuation of use of
Probably not related	There is evidence that the medical device was used, there is a more likely cause for the adverse event, the symptoms of the adverse event that occurred after discontinuing use of the medical device disappear or are ambiguous, and reuse of the medical device (if reuse is possible) (Only conducted) If the results do not show adverse event symptoms or are ambiguous
Definitely not related	If the relevant medical device was not used, the temporal sequence between the use of the relevant medical device and the occurrence of an adverse event is not reasonable, or there is another obvious cause for the adverse event.
Unknown	If the information is insufficient or conflicting, a decision cannot be made and it cannot be supplemented or confirmed.

*** The following criteria can be considered when evaluating causal relationships.**
Re-occurrence of adverse events as a result of re-application

Abnormal cases disappear as a result of discontinuation of application
(Symptoms disappear when the suspected medical device is discontinued without other medical intervention or treatment)
•Whether or not it is known to be a medical device adverse reaction from a medical device of the same class
•Biological probability
Absence of other possible factors – concomitant medications or diseases
•Typical medical device adverse reactions

2.4.2 Measures to be taken when adverse events occur

1) Adverse event training: The test director shall provide training to the test personnel, subjects, or agents on all adverse events that may occur after using the clinical trial medical device, and provide training to report all phenomena that occur after use.
2) If an adverse event occurs, ensure that the patient immediately receives necessary examination and treatment from the doctor in charge. In the event of a serious adverse medical device reaction, the clinical trial for the subject concerned shall be stopped and prompt and appropriate action shall be taken in accordance with “15.5 Report of Serious Adverse Events”.

2.4.3 Follow-up of medical device adverse reactions

Investigators must follow up on subjects who have experienced an adverse reaction to a medical device until symptoms disappear or the condition stabilizes, and if requested by the sponsor, a report on the subsequent progress of the adverse event must be submitted.

2.4.4 Treatment when symptoms worsen

13. Discontinuation criteria presented in “Criteria for discontinuation and withdrawal” ○4If the subject experiences an adverse event (AE), adverse medical device event (ADE), or serious adverse event (SAE) that makes it difficult to proceed with the clinical trial; ○5If other investigators determine that the test should be stopped, the application should be stopped immediately and replaced with an appropriate treatment regimen to ensure the safety of the subjects.

2.5 Reporting of serious adverse events

2.5.1 Definition of Serious Adverse Events

Serious adverse events refer to any of the following adverse events occurring due to medical devices used in clinical trials.
- When it causes death or threatens life
- When hospitalization or extension of hospitalization period is necessary
- Causes persistent or significant disability or functional decline
- If it causes congenital deformities or abnormalities

The term “life-threatening case” above refers to an event in which the subject is at immediate risk of death at the time the adverse event occurs.

Significant medical events that are not immediately life-threatening and do not result in death or hospitalization, but which, based on appropriate medical diagnosis, endanger the subject or require intervention to prevent the outcomes listed in the above definition, should also be considered serious adverse events.

If the subject visits the emergency room and the treatment time is 24 hours, the criteria for hospitalization are considered met. If hospitalization is scheduled before the first clinical trial medical device application (0w) or is due to a pre-existing disease, the hospitalization criteria are considered met. It is not considered an adverse event or serious adverse event. Elective surgery and subsequent hospitalization in the absence of adverse events are also not considered serious adverse events.

However, if hospitalization is unplanned or is the result of an adverse event, it is considered a serious adverse event.

If a situation occurs that is medically considered to have a significant impact on the subject's well-being and health, even if it is not a situation listed above, it is decided whether to consider it a serious adverse event based on the medical judgment of the doctor in charge and related experts, and accordingly. Take appropriate action accordingly.

2.5.2 Reporting procedures for serious adverse events/adverse medical device reactions

During this clinical trial, the principal investigator and the person in charge of the study must make every effort to ensure patient safety, and in the event of an unexpected serious adverse event/adverse medical device reaction, a reporting system must be established to take prompt and appropriate action to minimize adverse events.

When a serious adverse event/adverse medical device reaction occurs during a clinical trial, the duties of each person in charge are as follows.

- Duties of the Institutional Review Board

If a serious adverse event/adverse medical device reaction is reported, the Institutional Review Board must take necessary measures, such as recommending suspension to the trial director for part or all of the clinical trial.

- Obligations of test personnel

If a serious adverse event/adverse medical device reaction occurs during the conduct of a clinical trial, the person in charge of the study must immediately report it to the study director and sponsor

- Obligations of the client

i. The sponsor reports all serious and unexpected medical device adverse reactions to the investigator, the review committee (applicable only in cases where the study director did not report to the review committee or there is a need to change the reported details), and the Minister of Food and Drug Safety. It must be reported within the deadline according to the classification.

ii. Cases that cause death or threaten life: Within 7 days from the date the client receives or becomes aware of the relevant fact. In this case, the sponsor must additionally report detailed information on the medical device adverse reaction within 8 days from the initial reporting date.

iii. In case of other serious and unexpected medical device adverse reactions: Within 15 days from the date the sponsor received the report or became aware of the relevant fact.

1) If there is additional information about the medical device adverse reaction reported in accordance with 1), the sponsor must report it until the medical device adverse reaction is terminated (refers to when the medical device adverse reaction disappears or follow-up investigation becomes impossible)

2) If the sponsor wishes to report a medical device adverse reaction to the Minister of Food and Drug Safety according to 1), the medical device adverse reaction report according to Form No. 56 and the attached paper reported by the test director according to Subparagraph 8, Item 3) A rapid report on medical device adverse reactions in accordance with Form No. 55 must be attached and submitted.

- Obligations of the test director

1) The study director shall report all serious adverse events (excluding those that do not need to be reported immediately in the clinical trial plan or clinical investigator data sheet) as a medical device adverse reaction rapid report according to Form No. 55 within the period specified in the

clinical trial protocol. It must be reported to the client. In this case, the test director must use the subject identification code instead of the subject's personal information, such as the subject's name, resident registration number, and address, in order to protect the confidentiality of the subject's personal information. If there are guidelines for reporting adverse events, follow these.

2) The principal investigator must report adverse events or abnormal laboratory test results separately determined in relation to safety evaluation in the clinical trial protocol to the sponsor according to the reporting method established in the clinical trial protocol within the period specified in the clinical trial protocol.

3) When reporting a case of death, the principal investigator must submit additional information such as an autopsy report (only applicable to cases where an autopsy was performed) and a death certificate to the sponsor and review committee.

2.5.3 Follow-up of medical device adverse reactions and serious adverse events/medical device adverse reactions

Adverse medical device reactions and serious adverse events/adverse medical device reactions should be followed until they resolve, reach a stable state, or are no longer clinically significant when determined by the investigator.

3. Subject consent form

3.1 Consent Explanation and Consent Form

When conducting this clinical trial, the clinical trial director and clinical trial manager must fully explain to the subjects the study content, effects of the research medical device, and adverse events in advance, obtain the subject's consent, fill out a consent form, and indicate the date of consent acquisition in the case record. Write it down.

See Appendix 1. Subject Consent Statement Written Consent Form

4. Provisions for compensation to victims

See Appendix 2. Provisions on Compensation for Victims

5. Matters related to treatment of subjects after clinical trial

Subjects who drop out of the clinical trial or do not respond are instructed to receive other appropriate treatment, and subjects who have completed the clinical trial are allowed to receive treatment at any time according to the instructions of their doctor in preparation for the occurrence of unexpected delayed adverse events. If compensation is required due to an adverse reaction to a medical device, compensation will be made in accordance with Appendix 2. Victim Compensation Protocol.

6. Measures to protect the safety of subjects

6.1 Clinical trial implementation agency

The head of the implementing agency must be equipped with the clinical laboratory, equipment, and professional personnel necessary for the conduct of the clinical trial at each stage of the clinical trial, and must make thorough preparations to conduct the clinical trial appropriately.

6.2 Institutional Review Board, IRB

The clinical trial review committee must protect the rights, safety, and welfare of subjects and review whether the reasons for participation in clinical trials by subjects in vulnerable environments are reasonable.

In carrying out its duties, the Clinical Trial Review Committee may decide whether to suspend the clinical trial if the subject's consent to participate in the trial was not properly obtained, if the clinical trial was not conducted in accordance with the clinical trial protocol, or if a serious adverse event/adverse medical device reaction occurred. Necessary measures, such as a suspension order

for part or all of the test, must be taken by the test director.

The Clinical Trial Review Committee may request the head of the clinical trial institution or the principal investigator to suspend the clinical trial if the clinical trial being conducted is conducted differently from the requirements or decisions of the review committee or if an unexpected serious risk occurs to the subjects.

If it is deemed necessary to protect the rights, safety, and welfare of the subject, the Institutional Review Board may provide additional information other than the information provided to the subject or the subject's representative in the process of obtaining consent, consent form, subject instructions, and other documented information. The requester may be requested to provide to the subject.

6.3 Tester

Investigator refers to the principal investigator, person in charge of testing, and clinical trial coordinator.

1) Investigator’s duty to protect subjects

A. All medical decisions related to clinical trials on subjects are made by a principal investigator or investigator with the qualifications of a doctor, dentist, or oriental medical doctor.

B. Even during or after the clinical trial, the principal investigator must ensure that subjects receive appropriate medical treatment for any adverse events that occur during the clinical trial (including abnormalities in clinically meaningful laboratory test results), and the principal investigator must ensure that the principal investigator is aware of them. If the subject's concurrent disease requires medical treatment, the subject must be informed of this.

C. If the subject has a attending physician, the principal investigator may obtain the subject's consent and inform the attending physician of the subject's participation in the clinical trial.

D. If a subject withdraws from participation in a clinical trial before completion of the clinical trial, he or she does not need to disclose the reason, but the principal investigator must make efforts to confirm the reason to the extent that it does not infringe on the subject's rights.

6.4 Clinical trial sponsor

1) Quality assurance of clinical trials and quality control of clinical trial data

A. The sponsor must prepare the standard operating instructions for quality assurance of clinical trials and quality control of clinical trial data (hereinafter referred to as “sponsor standard operating instructions”) so that data related to the clinical trial can be generated, recorded, and reported in accordance with the clinical trial protocol and clinical trial management standards. ”) must be prepared.

B. The sponsor must conduct quality control of clinical trial data at all stages of data processing to ensure the reliability and accuracy of clinical trial data.

C. To enable monitoring and inspection, the sponsor must obtain prior consent from those involved in the clinical trial to visit the clinical trial site and view the clinical trial's supporting data, supporting documents, and reports through the clinical trial protocol or a separate consent form to enable monitoring and inspection.

2) Clinical trial consignment agency

A. The sponsor may entrust all or part of the sponsor's work related to the clinical trial to a clinical trial consignment agency, but the sponsor is responsible for managing the quality and accuracy of the clinical trial data.

B. The clinical trial consignment agency must ensure quality of the entrusted clinical trials and manage clinical trial data.

C. The entrustment according to A. must be made in a document containing the details of the specific work to be entrusted.

D. The clinical trial consignment agency must perform the entrusted work in accordance with the clinical trial management standards regarding the sponsor's duties and tasks.

6.5 Changes in clinical trial protocol

After the clinical trial protocol has been approved by the Institutional Review Board and the Minister of Food and Drug Safety, if the clinical trial protocol is changed due to extensive testing procedures, increased risk, changes in subject selection criteria, or additional safety information, the clinical trial protocol may be changed. Approval from the review committee and the Minister of Food and Drug Safety is required.

When revising the clinical trial protocol, the date of revision, reason for revision, content of revision, etc. must be recorded and stored.

Investigators must not conduct a clinical trial differently from the protocol before the change is approved by the Institutional Review Board and the Minister of Food and Drug Safety, except in cases where it is necessary to remove immediate risk factors to the subject. If such changes to the protocol are made prior to obtaining Institutional Review Board approval to eliminate immediate risk to subjects, the Institutional Review Board (for subsequent review approval), the sponsor, and the sponsor must be submitted to the Minister of Food and Drug Safety as soon as possible. Additionally, a document approved by the Chairman or Secretary of the Clinical Trial Review Committee must be sent to the sponsor.

Minor modifications or specifications that do not affect the clinical trial do not necessarily require approval and require administrative changes.

7. Other matters necessary to conduct clinical trials safely and scientifically

7.1 Compliance with the Declaration of Helsinki and medical device clinical trial conduct standards

This clinical trial is conducted in compliance with the ethical principles based on the “Declaration of Helsinki” and the “Standards for Conducting Clinical Trials of Medical Devices.”

7.2 Clinical trial implementation agency

The head of the implementing agency must be equipped with the clinical laboratory, equipment, and professional manpower necessary for the conduct of the clinical trial at each stage of the clinical trial, and must make complete preparations to conduct the clinical trial appropriately.

7.3 Institutional Review Board (IRB)

This clinical trial is reviewed by the clinical review committee of the clinical trial institution from the viewpoint of ethical, scientific, and medical validity regarding the suitability of the clinical trial.

7.4 Matters pertaining to the protection of human rights of subjects

When selecting a subject, the clinical trial director or person in charge of the clinical trial shall consider the subject's health status, symptoms, age, gender, ability to consent, relationship of dependence with the clinical trial director, etc., based on aspects of human rights protection and selection and exclusion criteria, and other clinical trials. We carefully consider recommending participation in clinical trials after considering whether or not to participate

Subject registration is done using a subject identification code, and sufficient consideration is given to protecting the privacy of the subject's name, disease, etc.

7.5 Confidentiality

7.5.1 Subject confidentiality

The identity of all subjects is kept confidential and confirmed during recording and evaluation by the subject's unique number assigned during the test. Inform subjects that all test data will be stored on a computer and treated as strictly confidential. The signed subject consent form is kept by the clinical trial director or person in charge.

7.5.2 Data confidentiality

By signing this protocol, the investigator acknowledges that all information provided by the sponsor will be kept confidential. In addition, when disclosing such information to the review committee or the Ministry of Food and Drug Safety, it is acknowledged that the relevant information must be provided after fully understanding the confidentiality of the information.

7.6 Provision of information and consent to subjects

Prior to the clinical trial, the clinical trial director or clinical trial manager shall sufficiently explain the contents of the following items a) to b) to the subject and confirm that he or she fully understands the relevant contents. Obtain written consent according to doctor's wishes. If the subject is judged to lack the ability to consent, he or she cannot be the subject of a clinical trial.

Except in cases where there is a special decision by the clinical trial institution, one copy of the written consent form, including the consent statement, is distributed to the subject.

<Content explained to subjects prior to starting clinical trial>

In the process of obtaining consent, the following information must be written in the information provided to the subject or the subject's representative, consent form, subject instructions, and other documented information.

A) The fact that clinical trials are conducted for research purposes
B) Purpose of clinical trial
C) Information on medical devices for clinical trials and probability of being randomly assigned to the test group or control group
D) Various tests or procedures that subjects will undergo in clinical trials
E) Matters to be observed by the subject
f) The fact that it is an unverified clinical trial
g) Risks or inconveniences expected to be caused to subjects (including fetuses when targeting pregnant women, and infants and young children when targeting lactating women)
h) If there is an expected benefit or there is no expected benefit to the subject, that fact
I) Other treatment methods or types that the subject can choose and the potential risks and benefits of those treatment methods
j) Compensation or treatment method to be given to the subject if damage related to the clinical trial occurs
k) If there is a financial compensation that the subject will receive by participating in the clinical trial, the expected amount and that this amount will be adjusted according to the degree or period of participation in the clinical trial
l) Costs expected for subjects by participating in clinical trials
m) The fact that the subject's decision to participate in the clinical trial must be voluntary, and that the subject may refuse to participate in the clinical trial or give up participation at any time during the clinical trial without loss of the benefits originally received.
H) Monitoring personnel in accordance with Item 8 of the Clinical Trial Management Standards, persons conducting inspections in accordance with Item 8 of the Clinical Trial Management Standards, the review committee, and the Minister of Food and Drug Safety verify the clinical trial conduct procedures and quality of data in accordance with relevant laws and regulations. In order to do so, the fact that the subject's medical records can be viewed to the extent that the confidentiality of the subject's personal information is protected, and that the signature of the subject or the subject's representative on the consent form allows the inspection of such data
o) The fact that records that can identify the subject's identity will be protected as confidential, and that if the results of the clinical trial are published, the subject's identity will be kept confidential.
e) The fact that the subject or the subject's representative will be notified in a timely manner if new information is obtained that may affect the subject's continued participation in the clinical trial.
Further) Who should be contacted if you wish to obtain additional information about the clinical trial and the rights and interests of the subjects, or if damage related to the clinical trial occurs

R) Cases where a subject's participation in a clinical trial is suspended during a clinical trial and the reasons for this

M) Subject's expected participation period in the clinical trial

B) Approximate number of subjects participating in clinical trials

7.7 Monitoring and Audit

7.7.1 Monitoring

Monitors consult with investigators regarding actual clinical trial conduct and compliance with protocol/GCP/all applicable regulatory requirements.

Investigators will permit monitors to periodically review all CRFs and corresponding supporting documentation (e.g., medical, hospital, and laboratory records of individual trial participants, etc.) at mutually convenient times during and after completion of the clinical trial. Therefore, monitors can directly view these records.

Monitoring visits provide an opportunity to evaluate trial progress, verify the accuracy and completeness of CRF records, ensure compliance with all protocol requirements/applicable regulations/investigator obligations, and resolve any discrepancies in trial records.

7.7.2 Audit and inspection

The investigator allows audits of this clinical trial and inspections by the Ministry of Food and Drug Safety to auditors commissioned by Nunaps Co., Ltd. The main purpose of inspections and inspections is to ensure that the rights, safety, and welfare of registered subjects are protected, or that registered subjects (i.e., who sign consent forms and undergo clinical trial procedures) are suitable for clinical trials, as well as to determine whether medical treatment for clinical trials is available. Verifies that all information pertinent to the device evaluation is processed/reported in compliance with the planned preparation, protocol, institutional and IRB SOPs, GCP, and applicable regulatory requirements. Investigators are provided with direct access to all clinical trial documents, supporting records, and supporting data. When the Ministry of Food and Drug Safety notifies the intention to conduct an inspection, the investigator must immediately notify Nunaps Co., Ltd.

7.8 Characteristics of supporting data

The following are defined as supporting data.

1) Supporting documents, data and records (instructions, consent forms, medical examination records, clinical examination records, records kept in the inspection department involved in clinical trials, etc., records of receipt and payment of medical devices for clinical trials, etc.)

2) Various information recorded in basic records or certified copies of clinical findings, observations, and other activities in clinical trials, which are necessary for reproduction and evaluation of the realistic progress of clinical trials

7.9 Data management

The monitor will check the consistency of the case record and basic data and the appropriateness of the case report information and quickly retrieve the case record. Additionally, the person in charge of data management checks the appropriateness of the contents of the case record, whether the contents are accurately entered into the computer, and whether there are any logical contradictions on the computer.

If there are inconsistencies in supporting data, inappropriateness of written information, or ethical contradictions, the data management manager shall review the validity of the relevant items with the clinical trial director and, if necessary, correct the case record. Nunaps Co., Ltd. declares data lock after confirming that there are no abnormalities in the case record and final data through the data management manager, clinical trial director, and clinical trial manager.

7.10 Quality assurance for data

Nunapse Co., Ltd. (or a designated clinical trial agency) ensures that database quality control

procedures are followed, including that investigators review data entered into the CRF for completeness and accuracy according to standard operating procedures.

7.11 Good Clinical Practice

The procedures specified in this protocol are written to ensure that clinical trial sponsors and investigators adhere to the fundamental spirit of GCP and the Declaration of Helsinki in conducting, evaluating, and recording the results of this trial. This test shall be conducted in accordance with KGCP and related regulations.

7.12 Use and management of medical devices for clinical trials

Medical devices for clinical trials are managed by a person designated by the head of the relevant clinical trial institution, or by a delegated person among the principal investigators or trial managers participating in the clinical trial. Medical devices for clinical trial use must be handled and stored as described in the description and include the phrase “for clinical trial use.” The manager of medical devices for clinical trials must perform tasks such as acquisition, inventory management, and return of medical devices used in clinical trials and maintain related records.

7.13 Supply and handling of medical devices for clinical trials

1) The sponsor must not supply medical devices for clinical trials to managers, etc. before obtaining approval from the review committee and the director for the clinical trial protocol.
2) The sponsor must have a documented procedure for how managers, etc. handle and store clinical trial medical devices, and these procedures include appropriate and safe handling, storage, return of unused clinical trial medical devices from subjects, and Methods for returning items to the requester are included.
3) Medical devices for clinical trials must be supplied in a timely manner, and records must be maintained regarding supply to the clinical trial institution, acquisition by the clinical trial institution, and return and disposal from the clinical trial institution.
4) The sponsor must establish and document a recall system for medical devices for clinical trials due to problems such as failure in the medical devices for clinical trials, completion of clinical trials, or expiration of the period of use.

7.14 Description of the clinical trial plan to the clinical trial director and clinical trial manager

Before commencing a clinical trial, the clinical trial sponsor explains the contents of the clinical trial plan to the clinical trial coordinator, principal investigator, clinical trial manager, clinical trial coordinator, and clinical trial medical device manager.

7.15 Compliance with clinical trial plan agreement

The clinical trial director agrees on compliance with the clinical trial plan. To ensure the above agreement, the clinical trial director signs and dates the clinical trial protocol agreement of this clinical trial protocol.
The principal investigator and person in charge of testing must conduct clinical trials in compliance with the protocol approved by the Institutional Review Board and the Minister of Food and Drug Safety

7.16 Modification of clinical trial protocol

If you wish to obtain approval for a clinical trial or conduct a change in an approved clinical trial, obtain approval for changes to the clinical trial plan or change plan from the IRB of the relevant institution and the Minister of Food and Drug Safety for each stage of the clinical trial. In addition, the principal investigator must sign and date a separate agreement document to ensure agreement on the revised clinical trial protocol or case record and proceed with the clinical trial in compliance with the revised and approved clinical trial protocol. However, only in the following cases can a clinical trial be

conducted differently from the original clinical trial protocol before receiving approval for the clinical trial change protocol.

1) When immediate risk to the subject must be removed

2) When matters related to administrative procedures need to be changed, such as a change in monitor personnel, a change in test manager, or a change in emergency contact phone number, etc.

For changes implemented without obtaining prior approval from the review committee for the change plan due to the need to remove immediate risk factors that occurred to the subject, the clinical trial director must provide the sponsor with a document recording the facts and reasons for implementation and the change plan as soon as possible. , must be submitted to the review committee of the testing institution and the Minister of Food and Drug Safety for agreement and approval, respectively.

7.17 Suspension or discontinuation of clinical trials

- Principal Investigator

1) If the study director terminates or suspends the clinical trial early without prior agreement with the sponsor, the study director must immediately notify the sponsor and the review committee of this fact and submit a detailed written explanation for the early termination or suspension.

2) If the sponsor terminates or suspends the clinical trial early, the principal investigator must immediately notify the review committee of this fact and submit a detailed written explanation for the early termination or suspension.

3) If the review committee terminates or suspends a clinical trial early, the principal investigator must immediately notify the sponsor of this fact and submit a detailed written explanation for the early termination or suspension.

4) If the clinical trial is terminated or stopped early in accordance with regulations from 1) to 3), the principal investigator must immediately notify the subject of this fact and ensure that appropriate measures and follow-up investigations are carried out.

If the following cases occur, the sponsor will review whether or not to continue the clinical trial based on the relevant clinical trial plan at the clinical trial implementation institution.

1) When a change in the clinical trial plan is necessary but the test institution is unable to respond

2) When the clinical trial sponsor is unable to accept a modification order issued by the head of the testing facility based on the opinion of the clinical review committee of the testing facility

3) When the head of the testing facility orders suspension of the clinical trial based on the opinion of the testing facility's Institutional Review Board that the clinical trial cannot be continued.

4) If the testing institution commits a serious or continuous violation of the KGCP, this clinical protocol, or the clinical trial contract.

In addition, if the clinical trial sponsor decides to suspend or discontinue the clinical trial, he or she will promptly notify the head of the testing institution of the purpose and reason in writing.

When the head of a testing institution receives a notice from the clinical trial requestor to the effect of suspending or discontinuing a clinical trial, he/she promptly notifies the clinical trial director and the clinical review committee of the purpose and reason in writing.

When the clinical trial director receives a notification related to the suspension or discontinuation of a clinical trial from the clinical trial requestor through the head of the testing institution, he/she promptly notifies the subject to that effect and ensures appropriate treatment and follow-up.

When a clinical trial is stopped, the response to the subject follows “13.2.2 Handling of withdrawal.”

7.18 End of clinical trial

The end of this clinical trial is the date of the last visit of the last subject in the target number of cases. After the medical device application and observation stipulated in the clinical trial plan for the final subject is completed, the clinical trial director reports the completion of the clinical trial in writing to the

review committee of the testing institution. The sponsor reports the completion of the clinical trial to the Ministry of Food and Drug Safety within 20 days from the end date.

7.19 Result report and publication

All data and results generated during this clinical trial are owned by Nunaps Co., Ltd., and the clinical trial director and clinical trial manager prepare a report on the contents of the study regarding the results of the clinical trial conducted in accordance with this clinical protocol.
The test institution and its investigators must make prior arrangements with Nunaps Co., Ltd. prior to announcing clinical trial results, and must not publish or announce the results of the test institution without written consent from the sponsor.

7.20 Storage of Documents

A separate storage location should be prepared and security should be maintained to ensure that various data and records related to the conduct of clinical trials are well preserved. The storage period follows the following enforcement regulations of the Medical Device Act.
1) Certification confirmation/import certification and certification test related data: 3 years from the date of adjustment
2) Data related to the clinical trial: 3 years from the date of the clinical trial
The sponsor must inform the investigator in writing of the need for data preservation and the retention period. If the sponsor determines that data preservation is no longer necessary, the sponsor must notify the study director of this fact in writing. In addition, the storage period may be extended if directed by the Minister of Food and Drug Safety or if the test director determines it is necessary

7.21 Data provided to the testing institution by the clinical trial sponsor

1) Medical devices for clinical trials
2) Subject medical device user manual
3) Clinical trial plan, case record, serious adverse event report, subject consent statement and written consent form, clinical trial medical device receipt and payment record form, etc.