

Study Protocol and Statistical Analysis Plan

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Responsible Party	Yong-Min Ahn, MD, PhD, Department of Psychiatry, Seoul National University Hospital
Planned Study Start	June 2026
Planned Study Completion	December 2027
Planned Analysis Completion	within 6 months after study completion (target: June 2028)
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This document contains no names of research participants.

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1. Study Protocol

1.1 Administrative Information

IRB number and notification date: 2405-162-1540; 30 March 2026.

Sponsor: Seoul National University Hospital.

Principal Investigator: Yong-Min Ahn, MD, PhD, Department of Psychiatry, Seoul National University Hospital.

Planned study start: June 2026. Planned study completion: December 2027. Planned final statistical analysis: within 6 months after study completion (target: June 2028).

This public upload draft was prepared in English for ClinicalTrials.gov and is based on the IRB-approved Korean participant information sheet and consent form, version 2.0, with notification date 30 March 2026.

1.2 Background and Rationale

Nonsuicidal self-injury is the intentional injury of one's own body tissue without suicidal intent. It has become a clinically and socially important phenomenon and may occur across several psychiatric conditions, including mood and anxiety disorders. Established pharmacological treatments specifically targeting nonsuicidal self-injurious behavior remain limited.

Some individuals with nonsuicidal self-injury show biological and psychological similarities to behavioral addictions. Naltrexone is an opioid receptor antagonist with established clinical use in substance-related and behavioral addiction contexts. This trial evaluates whether naltrexone may improve nonsuicidal self-injurious behavior when compared with placebo, both in addition to usual psychiatric care.

1.3 Objectives

Primary objective: To determine whether naltrexone 50 mg once daily reduces the frequency of nonsuicidal self-injurious behavior compared with placebo during a 6-week treatment period.

Secondary objectives: To evaluate changes in self-injurious urges, depression, anxiety, eating-related symptoms, obsessive-compulsive drinking/craving-related symptoms adapted for this study, global clinical severity and improvement, suicidal ideation and behavior, smartphone-based ecological momentary assessment measures, treatment adherence, and safety outcomes.

1.4 Study Design

This is a multicenter, randomized, double-blinded, placebo-controlled, parallel-group clinical trial. A total of 150 participants with nonsuicidal self-injury will be enrolled, with 75 participants per group. Participants will be randomized in a 1:1 ratio to receive either naltrexone plus treatment as usual or placebo plus treatment as usual for 6 weeks.

Participants will complete five study visits including screening, baseline, week 2, week 4, and week 6. The allowable visit window after baseline is ± 3 days. The planned study start is June 2026 and the planned study completion date is December 2027.

1.5 Study Population

The study population consists of individuals with nonsuicidal self-injurious behavior who are treated in inpatient or outpatient psychiatric settings at participating institutions and who are judged eligible by the investigator. Participants aged 18 years or younger may participate; however, they will be informed that the safety of the investigational product has not been established in individuals aged 18 years or younger.

Key Inclusion Criteria

- Clinically significant nonsuicidal self-injurious behavior.
- Ability to understand study procedures and comply with study visits, medication administration, and assessments.
- Written informed consent. For minors, consent/permission from a legal representative and assent from the participant will be obtained according to applicable requirements.

- For participants of childbearing potential, negative pregnancy testing when applicable and agreement to use appropriate contraception during participation.

Key Exclusion Criteria

- Current serious suicidal ideation or high suicide risk, as determined by the investigator.
- Current opioid use, opioid dependence, or use of opioid-containing medications.
- Use of disulfiram, thioridazine, or opioid analgesics during the study period.
- Known hypersensitivity to naltrexone or any component of the investigational product.
- Active liver disease, active hepatitis, or clinically significant hepatic impairment.
- Clinically significant renal impairment or other medical condition that would make participation unsafe.
- Pregnancy or breastfeeding.
- Any psychiatric or medical condition that, in the investigator's judgment, would interfere with study participation or make participation inappropriate.

1.6 Randomization and Blinding

Eligible participants will be randomly assigned in a 1:1 ratio to the experimental or comparator arm. Allocation concealment will be maintained through coded investigational products and restricted access to allocation information. Randomization procedures will be implemented by designated personnel independent from clinical outcome assessment.

The trial will be conducted under double-blind conditions. Participants and the investigators/outcome assessors who evaluate clinical outcomes will not know the assigned treatment until the study is completed and final analyses are performed. Emergency unblinding may occur if a serious adverse event or other clinically urgent situation requires knowledge of the treatment assignment for participant safety.

1.7 Investigational Product and Concomitant Treatment

Investigational product: Whanin Naltrexone Tab. 50 mg; active ingredient: naltrexone hydrochloride 50 mg; manufacturer: Whanin Pharm. Co., Ltd.

Experimental arm: Participants will take oral naltrexone 50 mg once daily for 6 weeks, in addition to usual psychiatric treatment.

Placebo comparator arm: Participants will take matching placebo once daily for 6 weeks, in addition to usual psychiatric treatment.

Participants will be asked to take the investigational product once daily, preferably at a similar time each day, complete a medication diary, and return all unused medication and containers at each applicable visit. Concomitant medications and non-pharmacological treatments will be recorded throughout the study.

The following medications are prohibited during study participation: disulfiram, thioridazine, and opioid analgesics. Other medications may be used according to clinical judgment and will be recorded.

1.8 Outcome Measures

Primary outcome: Change in the number of nonsuicidal self-injury episodes during the past 2 weeks from baseline to week 6, assessed through clinical interview and study-specific self-injury assessment procedures.

Secondary and exploratory outcomes include: modified OCDS, MADRS, HAM-A, PHQ-9, GAD-7, EDE-Q, CGI-S, CGI-I, C-SSRS, clinician-rated severity of nonsuicidal self-injury, ISAS, CTQ, DSHI, medication diary/adherence, and smartphone app-based ecological momentary assessment data including weekly PANAS and Modified OCS and daily mood, exercise, and sleep ratings.

1.9 Study Procedures and Schedule

The study visit schedule is summarized below. After the baseline visit, week 2, week 4, and week 6 visits may be scheduled within +/-3 days.

Procedure / Assessment	Screening	Baseline	Week 2	Week 4	Week 6
Informed consent	X				

Procedure / Assessment	Screening	Baseline	Week 2	Week 4	Week 6
Randomization		X			
Investigational product prescription		X	X	X	
Investigational product return			X	X	X
Eligibility assessment	X	X			
Demographics, medical and psychiatric history	X				
Concomitant medication review	X	X	X	X	X
Concomitant non-pharmacological therapy review	X	X	X	X	X
Number of self-injury episodes during the past 2 months	X				
Clinician-rated Severity of Nonsuicidal Self-Injury		X			
ISAS, CTQ, and DSHI		X			
Number of self-injury episodes during the past 2 weeks		X	X	X	X
Modified OCS	X	X	X	X	X
MADRS, HAM-A, PHQ-9, GAD-7		X	X	X	X
EDE-Q		X			X
CGI-S		X	X	X	X
CGI-I			X	X	X
Medication diary		Provided	X	X	X
Smartphone app-based EMA	Weekly PANAS and Modified OCS; daily mood, exercise, and sleep assessments; event-based entries for self-injury urges or self-injury events during the study period				
C-SSRS		X	X	X	X
Physical examination, weight, BMI, vital signs	X	X	X	X	X
Adverse event assessment			X	X	X
Blood tests, urine tests, and electrocardiography	X				X

During the study, study staff may contact participants by telephone, SMS, or other communication methods to remind them of visits or encourage completion of study records. Participants will install a study smartphone application to complete self-report ecological momentary assessments. Time-based assessments include weekly affect ratings and craving/urge-related ratings and daily mood, exercise, and sleep ratings. Event-based entries may be completed when self-injurious urges or self-injurious behavior occur.

1.10 Safety Monitoring and Stopping Criteria

Safety will be monitored at study visits through adverse event assessment, C-SSRS evaluation, physical examination, weight, BMI, vital signs, blood tests, urine tests, and electrocardiography according to the schedule. Adverse events will be assessed for seriousness, severity, outcome, and relationship to the investigational product.

Known or anticipated adverse reactions to naltrexone include nausea, headache, dizziness, fatigue, nervousness, insomnia, anxiety, depressed mood, vomiting, and other symptoms. Participants will be instructed to contact the study team immediately if they experience an unwanted effect, injury, suspected adverse reaction, pregnancy, or possible pregnancy.

Study participation may be discontinued if consent is withdrawn, a serious adverse event occurs, the participant's medical condition worsens, the investigator judges that clinically significant suicide risk is present, protocol adherence is inadequate, or the investigator determines that continuing participation is inappropriate or unsafe.

1.11 Data Management and Confidentiality

Participants will be assigned study identification numbers. Records that can identify participants will be managed using appropriate confidentiality protections, including coded identifiers whenever feasible. Study records may be reviewed by authorized monitors, auditors, the institutional review board, and regulatory authorities as permitted by applicable laws and regulations.

Study data and records will be retained in secured storage for 3 years after study completion and then appropriately destroyed according to institutional procedures. Results may be posted in public databases and disseminated in publications or presentations only after removal of personal identifiers and anonymization as required.

1.12 Ethics and Dissemination

Participation is voluntary. Participants may refuse to participate or withdraw at any time without penalty or loss of benefits and without effects on their regular clinical care. Written informed consent will be obtained before study-specific procedures. The study will be conducted in accordance with applicable ethical principles, Good Clinical Practice, and institutional requirements.

The results of the study may be disseminated through ClinicalTrials.gov, peer-reviewed publications, conference presentations, and clinical study reports.

2. Statistical Analysis Plan

2.1 Timing of Analyses

The final statistical analysis will be performed after database lock and treatment unblinding. The planned analysis will be completed within 6 months after study completion, with a target date no later than June 2028, assuming study completion in December 2027.

2.2 Analysis Populations

- Intent-to-Treat Population: All randomized participants analyzed according to assigned treatment group.
- Safety Population: All randomized participants who receive at least one dose of investigational product, analyzed according to treatment actually received.
- Per-Protocol Population: Participants without major protocol deviations that could substantially affect the primary efficacy evaluation. This population may be used for supportive analyses.

2.3 General Statistical Principles

All statistical tests will be two-sided unless otherwise specified. Descriptive statistics will summarize baseline characteristics, treatment exposure, adherence, efficacy outcomes, and safety outcomes. Continuous variables will be summarized using mean, standard deviation, median, interquartile range, minimum, and maximum, as appropriate. Categorical variables will be summarized using counts and percentages.

The primary efficacy analysis will be conducted in the intent-to-treat population. The significance level for the primary endpoint will be set at 0.05. Secondary analyses will be interpreted as supportive or exploratory unless otherwise specified in the final statistical analysis plan.

2.4 Primary Efficacy Analysis

The primary endpoint is the change in the number of nonsuicidal self-injury episodes during the past 2 weeks from baseline to week 6. The primary comparison will evaluate the between-group difference in change from baseline between the naltrexone group and placebo group.

The primary endpoint will be analyzed using a regression model appropriate for the distribution of the endpoint. If analyzed as count data, Poisson or negative binomial regression may be used with adjustment for baseline frequency and study site as appropriate. If analyzed as a continuous repeated measure, a mixed model for repeated measures may be used with fixed effects for treatment group, visit, treatment-by-visit interaction, baseline value, and study site as appropriate. The final model specification will be defined before database lock and unblinding.

2.5 Secondary and Exploratory Analyses

Secondary clinical outcomes, including MADRS, HAM-A, PHQ-9, GAD-7, EDE-Q, CGI-S, CGI-I, modified OCDS, C-SSRS, and related measures, will be analyzed using models appropriate to the scale and distribution of each outcome. Repeatedly measured outcomes may be analyzed using mixed models for repeated measures.

Smartphone app-based ecological momentary assessment data will be summarized using within-person and between-person descriptive statistics. Exploratory analyses may evaluate treatment-related changes in daily mood, exercise, sleep, weekly affect, self-injurious urges, and event-based ratings related to self-injury.

2.6 Safety Analyses

Safety analyses will be conducted in the safety population. Adverse events will be coded and summarized by treatment group, seriousness, severity, outcome, and relationship to investigational product. Laboratory test results, urine test results, vital signs, weight, BMI, physical examination findings, electrocardiography findings, and C-SSRS results will be summarized descriptively by visit and treatment group.

2.7 Missing Data and Protocol Deviations

The extent and patterns of missing data will be summarized by treatment group. The primary analysis will use methods that appropriately account for missing outcome data under plausible missing-data assumptions. Sensitivity analyses may include multiple imputation, last observation carried forward, or complete-case analyses, depending on the final endpoint definition and observed data structure.

Major protocol deviations will be identified before database lock and unblinding whenever possible. Supportive analyses based on the per-protocol population may be performed to evaluate robustness of the primary efficacy findings.

2.8 Statistical Software

Statistical analyses will be performed using validated statistical software, such as SAS, R, or equivalent software. The software version used for the final analyses will be documented in the clinical study report or statistical output archive.