CLINICAL STUDY REPORT

1. TITLE PAGE

Study Title:	A phase 2 study of S-812217 in patients with major depressive disorder
Study Number:	1818A3731
Study Phase:	2
Study Design:	**Design:** Multicenter, double-blind, randomized, placebo-controlled, parallel-group **Control:** Placebo **Duration of Study Treatment:** 2 weeks **Dose:** 20 and 30 mg of S-812217 or placebo once daily **Participant Population:** Japanese patients (≥ 18 to ≤ 75 years of age) with major depressive disorder
Product Name:	S-812217
Indication:	Major depressive disorder
Study Initiated:	16 Jun 2020
Study Completed:	02 Sep 2021
Sponsor:	Shionogi & Co., Ltd. (Head Office) 3-1-8 Doshomachi, Chuo-ku, Osaka 541-0045, Japan +81-6-6202-2161
Sponsor's Responsible Medical Officer	Sponsor's Chief Medical Officer Juan Carlos Gomez, MD
The Person Responsible for The Study Report within The Sponsor (Signer*) ***: Signature under delegation by Chief Medical Officer**	Sponsor's Senior Medical Fellow Tsutae “Den” Nagata, MD, PhD, FFPM
GCP Statement:	This study was conducted in accordance with Good Clinical Practice (GCP). Essential documents will be retained in accordance with GCP.
Date of Report:	Amendment: 14 May 2024 Original: 24 Feb 2022

Confidentiality Statement

2. SYNOPSIS

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Study Title:
A phase 2 study of S-812217 in patients with major depressive disorder

Investigators and Study Centers: This study was a multicenter study conducted at 72 sites in Japan.

Publication (reference): Not applicable

Studied Period:
From 16 Jun 2020 to 02 Sep 2021

Phase of Development: 2

Objectives:

Objectives	Endpoints
Primary	
• To evaluate the superiority of S-812217 at 20 and 30 mg to placebo in patients with moderate or severe major depressive disorder	• Change from baseline in HAM-D17 total score at Day 15
Secondary	
• To evaluate the efficacy of S-812217 at 20 and 30 mg compared with placebo • To estimate the dose-response relationship for S-812217 • To evaluate the safety of S-812217 • To determine the PK of S-812217	• HAM-D17 total score and its change from baseline • Presence or absence of response by HAM-D17 score[a] • Presence or absence of remission by HAM-D17 score[b] • HAM-D17 subscale scores and their changes from baseline • CGI-I score and the presence or absence of its improvement • CGI-S score and the presence or absence of "normal, not at all ill" or "borderline mentally ill" • PGI-I score and the presence or absence of its improvement • PHQ-9 score and its change from baseline

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	• Time to termination of the study due to lack of efficacy from the start of administration • Time to worsening to 15 or more in HAM-D17 score from Day 15 • 8 domain scores and summary scores of SF-36 as well as their changes from baseline • ISI total score and its change from baseline • Sleep diary items • FEV1 and %VC by spirometry • Incidence of AEs/treatment-related AEs • Plasma S-812217 concentration
Exploratory	
• Mental status by voice analysis technology • Blood levels of biomarkers for major depressive disorder	• Voice analysis results • Endpoints for biomarkers are described in the operating procedure

AE = adverse event; CGI-I = Clinical Global Impression - Global Improvement; CGI-S = Clinical Global Impression - Severity of Illness; FEV1 = forced expiratory volume in 1 second; HAM-D17 = 17-item Hamilton Rating Scale for Depression; ISI = Insomnia Severity Index; PGI-I = Patient Global Impression of Improvement; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetics; SF-36 = 36-item Short Form Health Survey; %VC = percent vital capacity

a Response was defined as a reduction of ≥ 50% in baseline HAM-D17 score.

b Remission was defined as a score of ≤ 7 on the HAM-D17.

Methodology:

- This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in Japanese patients with major depressive disorder. The study schedule consisted of the following:
  - **Screening period (from obtaining informed consent to Visit 1 qualification):**
    The screening process began after the potential participant (for the potential participant aged < 20 years, he/she and his/her legally acceptable representative [parent, legal guardian, etc.]) signed the informed consent form (ICF). The eligibility of potential participants was confirmed.
  - **Treatment period (from Visit 1 qualification to completion of Visit 4 examination):**
    A 2-week double-blind period. At Visit 1, participants were stratified by

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the baseline 17-item Hamilton Rating Scale for Depression (HAM-D17) total score (< 25 vs ≥ 25) and sex to randomize 80 participants each to the S-812217 20 mg group, the S-812217 30 mg group, and the placebo group. Randomized participants took the assigned study drug once daily for 2 weeks (Days 1 to 14).

- **Follow-up period A (from completion of Visit 4 examination to completion of Visit 10 examination):**
  A 6-week double-blind period. Participants did not take the study drug.
- **Follow-up period B (after completion of Visit 10 examination to completion of Visit 12 examination):**
  A 6-week double-blind period (unblinded for part of the sponsor's personnel). Participants did not take the study drug. Of the participants who had completed the follow-up period A, only those for whom further follow-up observation was possible in the opinion of the investigator or subinvestigator continued in the follow-up period B.

- If it was necessary to add or intensify treatment for the target disease in a participant in the opinion of the investigator or subinvestigator, the participant's participation in the study were to be discontinued before the treatment was added or intensified. However, this did not apply to patient's emergency situation.

Number of Participants (Planned and Analyzed):

Planned: 80 participants per group (240 participants in total)

Randomized: 250 (82 in the S-812217 30 mg group, 85 in the S-812217 20 mg group, 83 in the placebo group)

Analyzed for efficacy:

- Full analysis set (FAS): 242 (79 in the S-812217 30 mg group, 84 in the S-812217 20 mg group, 79 in the placebo group)
- Per protocol set (PPS): 235 (75 in the S-812217 30 mg group, 82 in the S-812217 20 mg group, 78 in the placebo group)

Analyzed for pharmacokinetic (PK) concentration: 163 (79 in the S-812217 30 mg group, 84 in the S-812217 20 mg group)

Analyzed for safety: 242 (79 in the S-812217 30 mg group, 84 in the S-812217 20 mg group, 79 in the placebo group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Japanese male or female outpatients aged ≥ 18 years and ≤ 75 years at the time of signing the ICF
- Patients who had been interviewed using Mini-International Neuropsychiatric Interview (M.I.N.I.) and diagnosed as having major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) and met the following 2 conditions:
  - The current episode had been ongoing for at least 8 weeks prior to the day of signing the ICF.
  - Duration of the current episode had been ≤ 12 months prior to signing the ICF.
- Patients with a HAM-D17 total score of ≥ 22 and a Patient Health Questionnaire-9 (PHQ-9) total score of ≥ 15 at Visit 1
- Forced expiratory volume in 1 second and percent vital capacity by respiratory function test (spirometry) were ≥ 70% and ≥ 80%, respectively.

2. Exclusion criteria

- Patients with treatment-resistant depression (no improvement in depressive symptoms even though at least 2 different antidepressants [excluding antipsychotics] had been administered for treatment of the existing depressive episode at adequate doses approved in Japan for 4 weeks) (Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [MGH ATRQ] was used for the evaluation)
- Patients who had been treated with therapies such as vagal nerve stimulation, electroconvulsive therapy, and transcranial magnetic stimulation for the current depressive episode
- Patients who had been interviewed using M.I.N.I. during the screening period and who had a complication or history of a disease classified into any of the following DSM-5 classifications in the opinion of the investigator or subinvestigator
  - Neurodevelopmental disorders
  - Schizophrenia spectrum and other psychotic disorders
  - Bipolar and related disorders
  - Psychological trauma- and stress-related disorders
  - Personality disorders
  - Obsessive-compulsive and related disorders
  - Anorexia nervosa, bulimia nervosa, binge-eating disorder
  - Neurocognitive disorders
  - Substance use disorders[a]
- Patients with any of the following diseases:
  - Epilepsy (including history of epilepsy)
  - Sleep apnea syndrome[b]

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- Chronic obstructive pulmonary disease
- Interstitial pneumonia
- Severe bronchial asthma
- Alveolar hypoventilation syndrome
- Chronic respiratory failure
- Pulmonary hypertension
- Clinically symptomatic bronchiectasis
- Patients with other chronic respiratory diseases and ineligible for the study in the opinion of the investigator

- Patients at suicidal risk who met any of the following criteria:
  - At Visit pre and within 12 months prior to Visit pre, patients who answered "Yes" to Suicidal Ideation Questions 4 or 5, or any of the Suicidal Behavior Questions (excluding questions about self-injurious behavior without suicidal intent) of the Columbia-Suicide Severity Rating Scale (C-SSRS)
  - At Visit 1, patients who answered "Yes" to Suicidal Ideation Questions 4 or 5 or to any of the Suicidal Behavior Questions (excluding questions about self-injurious behavior without suicidal intent) of the C-SSRS

a The following substance use disorders specified in DSM-5: alcohol, cannabis, hallucinogens (phencyclidine, and other hallucinogens), inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants (amphetamines, cocaine or other stimulants)

b If a participant met all of the following, the participant was suspected of having sleep apnea. The participant was to be excluded unless the suspicion was ruled out.

- Patients whose score of Japanese version of the Epworth Sleepiness Scale (JESS) was ≥11, and it was considered by the investigator or subinvestigator not attributable to major depressive disorder.
- Body mass index (BMI) of ≥ 30

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Test Product, Dose and Mode of Administration, Lot Number:

1. Test Product

S-812217 10 mg capsule (hard-gelatin capsule)

2. Dose and Mode of Administration

S-812217 30 mg group: 10 mg capsule × 3, orally

S-812217 20 mg group: 10 mg capsule × 2 and placebo capsule × 1, orally

3. Packaging Lot Number

Duration of Treatment:

Once daily for 2 weeks

Reference Therapy, Dose and Mode of Administration, Lot Number:

1. Reference Therapy

Placebo capsule (hard-gelatin capsule)

2. Dose and Mode of Administration

Placebo capsule × 3, orally

3. Packaging Lot Number

Statistical Methods:

Efficacy Analyses:

The FAS (defined as all participants randomly assigned to study drug who took at least 1 dose of study drug and had HAM-D17 measured at baseline and at least 1 time point after administration of study drug) was used for the primary analysis of the primary efficacy endpoint. As a supportive analysis for the primary analysis, the PPS was used.

All statistical tests were performed at a 2-sided significance level of 0.05 unless otherwise specified. Only in the primary analysis of the primary efficacy endpoint, a fixed sequence procedure was used to adjust for multiplicity for multiple testing. In

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the primary analysis, the change from baseline in HAM-D17 total score at Day 15 was compared between the S-812217 20 or 30 mg group and the placebo group using a mixed-effects model for repeated measures (MMRM), assuming that missing data was "missing at random". Using all available data obtained at Days 3 to 57, MMRM with the change from baseline as the response variable, with intervention group, time point, and the interaction between intervention group and time point as fixed effects, and with HAM-D17 total score at baseline and sex as covariates was applied. The MMRM did not assume a specific covariance structure for error term. If the algorithm did not converge in the above model, Heterogeneous AR (1), Heterogeneous Compound Symmetry, Compound Symmetry, and Variance Component were selected in this order as the covariance structure for the MMRM.

As the secondary endpoints, the percentages of presence or absence of response and remission by HAM-D17 score, both of which were predefined in the protocol, were compared between the S-812217 20 or 30 mg group and the placebo group for each Visit using inverse probability-weighted generalized estimating equation (IPW-GEE). Using all available data obtained at Days 3 to 57, IPW-GEE with intervention group, time point, and the interaction between intervention group and time point as fixed effects, and with the score at baseline and sex as covariates were applied.

Pharmacokinetic Analyses:

The plasma S-812217 concentration was listed by dosing regimen and Visit, along with the actual sampling time from the last dose. In addition, the plasma S-812217 concentration was graphically presented in an appropriate manner.

Safety Analyses:

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 Update. The number of AEs and treatment-related AEs as well as the number of participants with AEs and treatment-related AEs were tabulated by intervention group. Blood pressure, pulse rate, 12-lead electrocardiography (ECG) findings, laboratory measurements, and spirometry data at each time point were summarized by intervention group.

Summary of Results:

Efficacy:

- The adjusted mean (standard error) change from baseline in HAM-D17 total score at Day 15 was −8.33 (0.65) in the S-812217 30 mg group, −8.18 (0.63)

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in the S-812217 20 mg group, and −6.09 (0.64) in the placebo group. The difference in the adjusted mean between the S-812217 30 mg group and the placebo group was −2.24 (95% confidence interval [CI]: −4.03, −0.45) (p = 0.0146), and the difference in the adjusted mean between the S-812217 20 mg group and the placebo group was −2.09 (95% CI: −3.86, −0.33) (p = 0.0204). A statistical test adjusted for multiplicity using a fixed sequence procedure demonstrated a statistically significant difference in the primary efficacy endpoint in favor of S-812217 30 and 20 mg groups.

- The reduction in HAM-D17 total score was greater in the S-812217 30 and 20 mg groups than in the placebo group. Nominally significant improvement ($p < 0.05$) compared with the placebo group was observed in the S-812217 30 (Days 3 and 8) and 20 mg (Day 8) groups during the treatment period, but not during the follow-up period A except Day 43.
- The response rate (defined as a reduction of ≥ 50% in baseline HAM-D17 score) at Day 15 was higher in the S-812217 30 and 20 mg groups than in the placebo group, and a nominally significant difference ($p < 0.05$) compared with the placebo group was observed in the S-812217 30 mg group.
- The remission rate (defined as a score of ≤ 7 on the HAM-D17) at Day 15 was higher in the S-812217 30 and 20 mg groups than in the placebo group, but no nominally significant differences compared with the placebo group were observed in the S-812217 30 or 20 mg group.
- The reduction in HAM-D17 subscale scores was greater in the S-812217 30 and 20 mg groups than in the placebo group, but no nominally significant differences compared with the placebo group were observed in the S-812217 30 or 20 mg group at Day 15 except in insomnia symptoms score. In insomnia symptoms score at Day 15, nominally significant differences ($p < 0.05$) compared with the placebo group were observed in the S-812217 30 and 20 mg groups, but not during the follow-up period A.
- The proportion of participants with improvement (assessed as “very much improved” or “much improved”) by Clinical Global Impression - Global Improvement (CGI-I) at Day 15 was higher in the S-812217 30 and 20 mg groups than in the placebo group, but no nominally significant differences compared with the placebo group were observed in the S-812217 30 or 20 mg group.
- The proportion of participants assessed as “normal, not at all ill” or “borderline mentally ill” by Clinical Global Impression – Severity of Illness

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(CGI-S) was higher in the S-812217 30 and 20 mg groups than in the placebo group during the treatment period, but not during the follow-up period A. No nominally significant differences compared with the placebo group were observed in the S-812217 30 or 20 mg group at Day 15.

- The proportion of participants with improvement (assessed as "very much better" or "much better") by Patient Global Impression of Improvement (PGI-I) at Day 15 was higher in the S-812217 30 and 20 mg groups than in the placebo group, but no nominally significant differences compared with the placebo group were observed in the S-812217 30 or 20 mg group.
- No nominally significant differences compared with the placebo group in change from baseline in PHQ-9 total score at Day 15 were observed in the S-812217 30 or 20 mg group.
- No nominally significant differences compared with the placebo group in change from baseline in 36-item Short Form Health Survey (SF-36) summary scores or 8-domain scores at Day 15 were observed in the S-812217 30 or 20 mg group except in general health perceptions score. In general health perceptions score at Day 15, nominally significant differences ($p < 0.05$) compared with the placebo group were observed in the S-812217 20 mg group, but not in the S-812217 30 mg group.
- The reduction in ISI total score at Day 15 was greater in the S-812217 30 and 20 mg groups than in the placebo group, and nominally significant differences ($p < 0.05$) compared with the placebo group were observed in the S-812217 30 and 20 mg groups.

Safety:

- No deaths or other serious treatment-emergent adverse event (TEAEs) were reported during the study.
- Treatment-emergent adverse events were reported in 43/79 (54.4%) participants in the S-812217 30 mg group, 46/84 (54.8%) participants in the S-812217 20 mg group, and 41/79 (51.9%) participants in the placebo group. Treatment-related AEs were reported in 26/79 (32.9%) participants in the S-812217 30 mg group, 27/84 (32.1%) participants in the S-812217 20 mg group, and 16/79 (20.3%) participants in the placebo group.
- Treatment-emergent adverse events during the study with an incidence of ≥ 5% in any of the groups were somnolence (17/79 [21.5%] in the S-812217 30 mg group, 10/84 [11.9%] in the S-812217 20 mg group, 5/79 [6.3%] in the

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placebo group, hereinafter in the same order), dizziness (7/79 [8.9%], 9/84 [10.7%], 3/79 [3.8%]), nasopharyngitis (6/79 [7.6%], 6/84 [7.1%], 4/79 [5.1%]), headache (4/79 [5.1%], 6/84 [7.1%], 3/79 [3.8%]), and nausea (3/79 [3.8%], 4/84 [4.8%], 4/79 [5.1%]). Of these AEs, treatment-related AEs were somnolence (17/79 [21.5%], 9/84 [10.7%], 3/79 [3.8%]), dizziness (7/79 [8.9%], 8/84 [9.5%], 2/79 [2.5%]), headache (1/79 [1.3%], 3/84 [3.6%], 3/79 [3.8%]), and nausea (1/79 [1.3%], 2/84 [2.4%], 1/79 [1.3%]).

- No severe TEAEs were reported during the study.
- A total of 2 TEAEs (dizziness and somnolence) leading to withdrawal of study drug were reported in 1/84 (1.2%) participant in the S-812217 20 mg group. Dizziness was moderate in severity, and somnolence was mild. Both of the events were resolved and considered treatment-related.
- The incidence of TEAEs of special interest that occurred during the study was higher in the S-812217 30 mg group (21/79 [26.6%]) and the S-812217 20 mg group (18/84 [21.4%]) than in the placebo group (8/79 [10.1%]). The most common TEAE of special interest was somnolence (17/79 [21.5%] in the S-812217 30 mg group, 10/84 [11.9%] in the S-812217 20 mg group, 5/79 [6.3%] in the placebo group, hereinafter in the same order), followed by dizziness (7/79 [8.9%], 9/84 [10.7%], 3/79 [3.8%]). The proportion of participants with somnolence increased in a dose-dependent manner. Most of the TEAEs of special interest were considered treatment-related. No TEAEs classified as respiratory failure or drug abuse and dependence were reported.
- No clinically notable trends were observed in laboratory values, vital signs, or electrocardiographic parameters.
- The Dependence Assessment Committee found no events suspected to be drug dependence or drug abuse.
- Based on spirometry data, no apparent effects of S-812217 on respiratory functions were observed.

Pharmacokinetics:

Plasma S-812217 concentrations in each dose group were comparable between Visit 3 and Visit 4, and plasma S-812217 concentrations at 30 mg dose tended to be higher than those at 20 mg dose.

CONCLUSIONS

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The efficacy of S-812217 at 30 and 20 mg for 2 weeks in patients with major depressive disorder was demonstrated, and no new safety issues were found in this study.		
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