2. SYNOPSIS

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Study Title:
A phase 3 study of S-812217 in patients with major depressive disorder consisting of randomized, double-blind, placebo-control part and extension, open-label, re-treatment part

Investigators and Study Sites: This study was a multicenter study conducted at 70 sites in Japan.

Publication (reference): Not applicable

Studied Period:
From 19 Feb 2022 to 16 May 2024

Phase of Development: Phase 3

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To verify the superiority of S-812217 to placebo in participants with depression, as measured by the change from baseline in HAM-D17 total score at Visit 4 (Day 15 ± 1) of Part A.	• Change from baseline[a] in HAM-D17 total score at Visit 4 (Day 15 ± 1) of Part A
Secondary	
Part A • To evaluate the efficacy of treatment with S-812217 for 14 days compared with placebo in participants with depression at each time point.	• Change from baseline[a] in HAM-D17 total score at each time point (except Visit 4 [Day 15 ± 1]) • Presence or absence of response[b] by HAM-D17 total score at each time point • Days from baseline[a] to the first response[b] by HAM-D17 total score

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	• Presence or absence of remission[c] by HAM-D17 total score at each time point • Days from baseline[a] to the first remission[c] by HAM-D17 total score • Change from baseline[a] in HAM-D17 subscale score at each time point • Days from baseline[a] to the first achievement of HAM-D17 total score ≤ 13 • Presence or absence of improvement in CGI-I score (assessed as "very much improved" or "much improved") at each time point • Presence or absence of improvement in CGI-S score (assessed as "normal, not at all ill" or "borderline mentally ill") at each time point • Change from baseline[a] in CGI-S score at each time point • Presence or absence of improvement in PGI-I score (assessed as "very much better" or "much better") at each time point • Change from baseline[a] in PHQ-9 total score at each time point • Eight domain scores and summary scores of SF-36 as well as their changes from baseline[a] at each time point • ISI total score and its change from baseline[a] at each time point

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• To evaluate the safety and tolerability of treatment with S-812217 for 14 days in participants with depression.	• Safety endpoints: AEs, blood pressure and pulse rate, 12-lead ECG, laboratory tests, C-SSRS, D-2-A (risk assessment of drug dependence and drug abuse), D-2-B (assessment of withdrawal symptoms), and DEQ-5
• To evaluate the number of days from the last dose in the treatment period to re-treatment and the number of participants with depression who required re-treatment.	• Days from the last dose in the treatment period to re-treatment • Presence or absence of re-treatment
• To determine the PK of S-812217 in participants with depression.	• Plasma S-812217 concentration
Part B • To evaluate the safety and tolerability of re-treatment with S-812217 in participants with depression.	• Safety endpoints: AEs, blood pressure and pulse rate, 12-lead ECG, laboratory tests, C-SSRS, and drug dependence assessment (D-2-A, D-2-B, and DEQ-5)
• To evaluate the required number of treatment cycles from the first treatment cycle of S-812217 during 1-year (52 weeks) follow-up in participants with depression.	• Number of treatment cycles of S-812217 in each participant (including the treatment in Part A)
• To evaluate the efficacy of re-treatment with S-812217 in participants with depression.	• HAM-D17 total score and its change from baseline[d] at each time point • Presence or absence of response[b] by HAM-D17 total score at each time point • Presence or absence of remission[c] by HAM-D17 total score at each time point

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	• HAM-D17 subscale scores and their changes from baseline[d] at each time point • Days from the last dose in the treatment period in each treatment cycle to re-treatment • Days from baseline[d] to the first response[b] by HAM-D17 total score • Days from baseline[d] to the first remission[c] by HAM-D17 total score • CGI-I score and presence or absence of its improvement at each time point • CGI-S score and presence or absence of its improvement at each time point • PGI-I score and presence or absence of its improvement at each time point • PHQ-9 score and its change from baseline[d] at each time point • Eight domain scores and summary scores of SF-36 as well as their changes from baseline[d] at each time point • ISI total score and its change from baseline[d] at each time point
• To determine the PK of S-812217 following re-treatment.	• Plasma S-812217 concentration
Exploratory	
• To evaluate the effect of S-812217 on sleep in participants with depression.	• Sleep diary endpoints
• To evaluate the effect of S-812217 on sleep/activity levels in participants with depression.	• Measurement of sleep/activity levels using a wearable device

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AE = adverse event; CGI-I = clinical global impression - global improvement; CGI-S = clinical global impression - severity of illness; C-SSRS = Columbia-suicide severity rating scale; D-2-A = Dependence-2A; D-2-B = Dependence-2B; DEQ-5 = drug effect questionnaire-5; ECG = electrocardiogram; 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 = Short Form Health Survey

a Baseline value in Part A was defined as the value obtained at Visit 1 (Day 1).

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

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

d Baseline value in Part B was defined as the value obtained at Visit 1 (Day 1) of each treatment cycle.

Methodology:

This study consisted of Part A (a randomized, double-blind, placebo-controlled part) and Part B (an extension, open-label, re-treatment part). Part A of this study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in Japanese participants with depression. Part B of this study was a multicenter, extension, open-label, re-treatment study in participants who had completed Part A.

Part A:

Part A consisted of a screening period (1 to 4 weeks), a treatment period (2 weeks), and a follow-up period (6 weeks), with a total study duration of 12 weeks. On Day 1 to Day 14 during the treatment period, participants received S-812217 or placebo once daily. In all periods of Part A, participants visited the study site for the scheduled assessments.

Part B:

Participants who consented to participate in Part B between Visit 9 and Visit 10 (Day 50 ± 2 and Day 57 ± 2) of Part A, and were determined to be eligible at Visit 10 (Day 57 ± 2) of Part A, entered Part B. Those who were not eligible for Part B at Visit 10 (Day 57 ± 2) of Part A were also allowed to enter Part B if they were found eligible by Visit 10 + 7 days of Part A. Part B consisted of a treatment period, a follow-up period, and a durability observation period. One treatment cycle of S-812217 was defined as a pair of treatment period (2 weeks) and follow-up period (6 weeks), and the number of treatment cycles was 6 at the maximum. Participants received the study intervention once daily on Day 1 to Day 14 of the treatment period. During the treatment period, participants visited the study site for scheduled assessments at all time points. During the follow-up period, participants received remote examinations by telephone, etc. on Day 29 ± 2, Day 43 ± 2, and Day 50 ± 2,

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and visited the study site for the scheduled assessments at Visit 4 (Day 22 ± 2), Visit 5 (Day 36 ± 2), and Visit 6 (Day 57 ± 2).

Participants who met the Criteria for Starting the Treatment Period of Part B at the final visit (Visit 10 [Day 57 ± 2]) of Part A entered the treatment period, and those who did not meet the criteria entered the durability observation period. At the end of the follow-up period (Visit 6 [Day 57 ± 2]) in each treatment cycle of Part B, whether to enter the treatment period or the durability observation period was determined in the same manner. During the durability observation period, assessments scheduled for Week 1 to Week 8 were repeated every 8 weeks. Participant who met the Criteria for Starting the Treatment Period of Part B at the specified visit during the durability observation period entered the treatment period within 1 week after the visit.

Criteria for Starting the Treatment Period of Part B

If a participant met both of the following conditions, the treatment cycle (treatment period) of Part B was started.

- Seventeen-item Hamilton Rating Scale for Depression (HAM-D17) total score ≥ 14
- Depressive episode persisted for 2 weeks or longer

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Number of Participants (Planned and Analyzed):

Planned:

Part A: The target number of randomized participants was 400 in total (200 each in the S-812217 and placebo groups).

Part B: The target number of participants completing at least 1 year (52 weeks) of evaluation after the initial dose in Part B was at least 100. The target number of participants consenting to the additional evaluation of sleep/activities using the wearable device Fitbit Charge 4 (Fitbit) was 96.

Part A:

Randomized: 412 (207 in the S-812217 group, 205 in the placebo group)

Analyzed for efficacy:

- Full analysis set (FAS):
  404 (205 in the S-812217 group, 199 in the placebo group)
- Per protocol set (PPS):
  378 (186 in the S-812217 group, 192 in the placebo group)

Analyzed for safety:

- Safety analysis set:
  404 (205 in the S-812217 group, 199 in the placebo group)

Analyzed for pharmacokinetics (PK):

- PK Concentration population:
  204 in the S-812217 group

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Part B:

Analyzed for efficacy:

- FAS:
  Cycle 1
  271 (128 in the S-812217/S-812217 group, 143 in the placebo/S-812217 group)
  Cycle 2
  213 (99 in the S-812217/S-812217 group, 114 in the placebo/S-812217 group)
  Cycle 3
  170 (76 in the S-812217/S-812217 group, 94 in the placebo/S-812217 group)
  Cycle 4
  147 (63 in the S-812217/S-812217 group, 84 in the placebo/S-812217 group)
  Cycle 5
  126 (55 in the S-812217/S-812217 group, 71 in the placebo/S-812217 group)
  Cycle 6
  99 (43 in the S-812217/S-812217 group, 56 in the placebo/S-812217 group)

Analyzed for safety:

- Safety analysis set:
  Cycle 1
  271 (128 in the S-812217/S-812217 group, 143 in the placebo/S-812217 group)
  Cycle 2
  213 (99 in the S-812217/S-812217 group, 114 in the placebo/S-812217 group)
  Cycle 3
  170 (76 in the S-812217/S-812217 group, 94 in the placebo/S-812217 group)
  Cycle 4
  147 (63 in the S-812217/S-812217 group, 84 in the placebo/S-812217 group)
  Cycle 5
  126 (55 in the S-812217/S-812217 group, 71 in the placebo/S-812217 group)
  Cycle 6
  99 (43 in the S-812217/S-812217 group, 56 in the placebo/S-812217 group)
- 1-year Followed Up population
  163 (74 in the S-812217/S-812217 group, 89 in the placebo/S-812217 group)

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Analyzed for PK:

- PK Concentration population:
  Cycle 1
  271 (128 in the S-812217/S-812217 group, 143 in the placebo/S-812217 group)
  Cycle 2
  213 (99 in the S-812217/S-812217 group, 114 in the placebo/S-812217 group)

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

Part A:

- Japanese male or female outpatients aged ≥ 18 years and ≤ 75 years at the time of signing the informed consent form (ICF).
- Patients who had been interviewed using Mini-International Neuropsychiatric Interview (M.I.N.I.) and had diagnosis of depression according to the diagnostic and statistical manual of mental disorders 5th edition (DSM-5), and who met the following 2 conditions:
  - The current episode had continued for at least 8 weeks prior to the day of signing the ICF.
  - Duration of current episode was ≤ 12 months at 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 (Day 1).
- Patients who were able to maintain the daily rhythm of eating evening meal or eating a light meal before bedtime and sleeping at night from the time of signing the ICF until the completion of the study.

Part B:

- Patients who had participated in Part A and had completed its treatment period and follow-up period.
- Patients who were able to maintain the daily rhythm of eating evening meal or eating a light meal before bedtime and sleeping at night from the time of signing the ICF until the completion of the study.

2. Exclusion criteria

Part A:

- Patients with serious hepatic disorder, renal disorder, cardiac disease, pulmonary disease, hematological disease, metabolic disease, etc.

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- Patients with treatment-resistant depression; no improvement in depressive symptoms even though at least 2 different antidepressants, except for antipsychotics, had been administered for treatment of an existing depressive episode at adequate doses approved in the country for 4 weeks or more. The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ) was evaluated only at Visit 1 (Day 1).
- Patients who had been treated with devices 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
- Patients with any of the following diseases:
  - Epilepsy (including history of epilepsy)
  - Sleep apnea syndrome
  - Interstitial pneumonia
  - Severe bronchial asthma
  - Alveolar hypoventilation syndrome
  - Chronic respiratory failure
  - Pulmonary hypertension
  - Patients with other chronic respiratory diseases and ineligible for the study in the opinion of a physician

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- 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 Question 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 (Day 1), patients who answered "Yes" to Suicidal Ideation Question 4 or 5 or to any of the Suicidal Behavior Questions (excluding questions about self-injurious behavior without suicidal intent) of the C-SSRS.
- Patients with known allergy to S-812217, allopregnanolone, or any related substances.

Part B:

- Patients considered by the investigator or subinvestigator to be inappropriate for participation in the re-treatment part due to unresolved adverse events (AEs) from Part A.
- Patients with serious hepatic disorder, renal disorder, cardiac disease, pulmonary disease, hematological disease, metabolic disease, etc.
- Patients with any of the following diseases:
  - Epilepsy (including history of epilepsy)
  - Sleep apnea syndrome
  - Interstitial pneumonia
  - Severe bronchial asthma
  - Alveolar hypoventilation syndrome
  - Chronic respiratory failure
  - Pulmonary hypertension
  - Patients with other chronic respiratory diseases and ineligible for the study in the opinion of a physician
- Patients at suicidal risk who met any of the following criteria:
  - In Part A, patients who answered "Yes" to Suicidal Ideation Question 4 or 5 or to any of the Suicidal Behavior Questions (excluding questions about self-injurious behavior without suicidal intent) of the C-SSRS.

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

- S-812217 capsules 30 mg for Part A
- S-812217 capsules 30 mg for Part B

S-812217 30 mg was orally administered once daily.

Duration of Treatment:

Part A: 14 days

Part B: 14 days per treatment cycle (the number of treatment cycles was 6 at the maximum)

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

- S-812217 capsules placebo

Placebo was orally administered once daily.

Statistical Methods:

Efficacy Analyses:

The primary endpoint was analyzed on the FAS and PPS. Secondary endpoints were analyzed on the FAS.

Primary Endpoint (Part A)

The change from baseline in HAM-D17 total score at Day 15 of Part A was compared between the S-812217 and placebo groups using a mixed effect model for repeated measures (MMRM). All available data from Day 3 through Day 57 were used in the MMRM which included the change from baseline as the response variable, intervention group, time point, and interaction between the intervention group and time point as fixed effects, and HAM-D17 total score at baseline, sex, and the presence or absence of prior drug for depressive episode as covariates. The MMRM did not assume a specific covariance structure for error term. Sensitivity analyses including tipping point analysis were performed for the primary endpoint on the FAS.

Secondary Endpoint (Part A)

For the continuous endpoints, the changes from baseline in the applicable score at each visit were compared between the S-812217 and placebo groups using MMRM. All available data at each visit were used in the MMRM which included the change from baseline in the applicable score as the response variable, intervention group, time point, and interaction between the intervention group and time point as fixed effects, and the applicable score at baseline, sex, and the presence or absence of prior

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drug for depressive episode as covariates. The MMRM did not assume a specific covariance structure for error term.

For the binary endpoints, the percentage of presence or absence of the applicable outcome measure at each visit was compared between the S-812217 and placebo groups using inverse probability weighted-generalized estimating equation (IPW-GEE). All available data at each visit were used for IPW-GEE which included intervention group, time point, and interaction between the intervention group and time point as fixed effects, and the applicable score at baseline, sex, and the presence or absence of prior drug for depressive episode as covariates.

Kaplan-Meier curves were presented for each intervention group and the intervention groups were compared for days from baseline to the first response by HAM-D17 total score, days from baseline to the first remission by HAM-D17 total score, days from baseline to the first achievement of HAM-D17 total score ≤ 13, and days from the last dose in the treatment period to re-treatment. Kaplan-Meier estimates were calculated for each group and compared between the groups by log-rank test. In addition, summary statistics were calculated for the participants with or without re-treatment, and the risk ratio and risk difference of re-treatment and their 95% CIs were calculated.

Secondary Endpoint (Part B)

For each treatment cycle, results were summarized by intervention group in Part A and for the whole participant population.

- Number of treatment cycles of S-812217 in each participant (including treatment in Part A)
  Summary statistics were calculated for the number of treatment cycles of S-812217 in each participant. In Part B, the same summary statistics were calculated for participants who completed 1-year follow-up.
- HAM-D17 total score and its change from baseline at each time point
  Summary statistics by time point were calculated for HAM-D17 total score and its change from the start of study intervention in each treatment cycle.
- Presence or absence of response by HAM-D17 total score at each time point
  For presence or absence of response by HAM-D17 total score, the number and percentage of participants were calculated for each time point in each treatment cycle.

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- Presence or absence of remission by HAM-D17 total score at each time point
  For presence or absence of remission by HAM-D17 total score, the number and percentage of participants were calculated for each time point in each treatment cycle.
- HAM-D17 subscale scores and their changes from baseline at each time point
  Summary statistics by time point were calculated for HAM-D17 subscale scores and their changes from the start of study intervention in each treatment cycle.
- Days from the last dose in the treatment period of each treatment cycle to re-treatment
  Kaplan-Meier estimates were calculated for the days from the last dose in the treatment period of each treatment cycle to re-treatment.
- Days from baseline to the first response by HAM-D17 total score
  Kaplan-Meier estimates were calculated for the number of days from the start of study intervention in each treatment cycle to the first HAM-D17 total score response.
- Days from baseline to the first remission by HAM-D17 total score
  Kaplan-Meier estimates were calculated for the number of days from the start of study intervention in each treatment cycle to the first HAM-D17 total score remission.
- Clinical global impression - global improvement (CGI-I) score and presence or absence of its improvement at each time point
  For CGI-I score and presence or absence of its improvement, the number and percentage of participants were calculated for each time point in each treatment cycle.
- Clinical global impression - severity of illness (CGI-S) score and presence or absence of its improvement at each time point
  For CGI-S score, its change from the start of study intervention in each treatment cycle, and presence or absence of its improvement, the number and percentage of participants were calculated for each time point in each treatment cycle.

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- Patient global impression of improvement (PGI-I) score and presence or absence of its improvement at each time point
  For PGI-I score and presence or absence of its improvement, the number and percentage of participants were calculated for each time point in each treatment cycle.
- PHQ-9 score and its change from baseline at each time point
  For PHQ-9 score and its change from the start of study intervention in each treatment cycle, the summary statistics were calculated for each time point.
- Eight domain scores and summary scores of Short Form Health Survey (SF-36) as well as their changes from baseline at each time point
  For 8 domain scores and summary scores of SF-36 as well as for their changes from the start of study intervention in each treatment cycle, the summary statistics were calculated for each time point.
- Insomnia severity index (ISI) total score and its change from baseline at each time point
  For ISI total score and its change from the start of study intervention in each treatment cycle, the summary statistics were calculated for each time point.

Safety Analyses:

Adverse events were classified by system organ class (SOC) and preferred term (PT) according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities (MedDRA), version 24.1.

The number of participants, number of events, and incidence of treatment-emergent AEs (TEAEs) were summarized by intervention group. Treatment-emergent AEs leading to death, serious TEAEs other than death, and TEAEs leading to treatment discontinuation were summarized in the same manner as TEAEs. The number of reported AEs were also presented. Treatment-emergent AEs whose causal relationship to the study intervention were not ruled out were regarded as treatment-related AEs, and treatment-related AEs were summarized in the same manner as TEAEs. For the summary of TEAEs by SOC and PT, the number and percentage of participants with AEs were presented for each intervention group. In addition, the summary by severity, outcome, and timing of onset were presented. Treatment-related AEs were also summarized in the same manner. The analyses for Part A were performed by intervention group and period, and the analyses for Part B were performed by

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intervention group in Part A, cycle (Cycle 1 to Cycle 6), and period (only for the treatment period and follow-up period).

For body weight, vital signs, 12-lead electrocardiogram (ECG), and laboratory test values, summary statistics were presented for each scheduled time point. For C-SSRS, the result for each question was summarized by intervention group and time point in a shift table, and were listed by participant. For Dependence-2A (D-2-A) and Dependence-2B (D-2-B) were listed by participant. For drug effect questionnaire-5 (DEQ-5), summary statistics were calculated for each question item at each time point.

Summary of Results:

Efficacy:

Primary Endpoint

The primary endpoint was the change from baseline in HAM-D17 total score at Day 15 of Part A. The primary efficacy endpoint was met for the FAS; the difference in adjusted means (95% CI) between the intervention groups (S-812217 – placebo) was −1.20 (−2.32, −0.08), indicating a statistically significantly greater improvement in the S-812217 group compared with the placebo group ($p = 0.0365$). The conclusion was confirmed with PPS; the difference in the adjusted means (95% CI) between the intervention groups (S-812217 – placebo) was −1.32 (−2.49, −0.16) ($p = 0.0259$).

Part A

Secondary Endpoints

- The mean changes from baseline in HAM-D17 total score were greater in the S-812217 group than in the placebo group at all time points. The difference in adjusted means (95% CI) between the intervention groups (S-812217 – placebo) was −1.52 (−2.16, −0.89) at Day 3 and −1.76 (−2.64, −0.88) at Day 8; nominally significantly greater change in the S-812217 group compared with the placebo group was observed already at Day 3 (first postbaseline observation) and Day 8 ($p < 0.05$).
- The response rate in HAM-D17 total score was higher in the S-812217 group than in the placebo group at all time points. The adjusted odds ratio (95% CI) was 8.27 (1.02, 66.78) at Day 3 and 2.44 (1.19, 4.97) at Day 8 with the S-812217 group achieving nominal significance versus placebo ($p < 0.05$).

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- The median time from baseline to the first response in HAM-D17 total score, censored when a participant discontinued, completed, or had a re-treatment, was not estimable in either intervention group. The Kaplan-Meier estimate of median (95% CI) time from baseline to the first response in HAM-D17 total score, censored when a participant discontinued or completed, was 78.0 (50.0, 148.0) days in the S-812217 group and 121.0 (66.0, 173.0) days in the placebo group (stratified log-rank test, $p = 0.4981$).
- The remission rate in HAM-D17 total score was higher in the S-812217 group than in the placebo group at all time points, with nominal significance ($p < 0.05$) at Day 29.
- The median time from baseline to the first remission in HAM-D17 total score, censored when a participant discontinued, completed, or had a re-treatment was not estimable in either intervention group. The Kaplan-Meier estimate of median (95% CI) time from baseline to the first remission in HAM-D17 total score, censored when a participant discontinued or completed, was 247.0 (170.0, 379.0) days in the S-812217 group and 337.0 (197.0, not estimated) days in the placebo group (stratified log-rank test, $p = 0.2807$).
- For all HAM-D17 subscale scores on a percentage scale, the adjusted mean changes from baseline were greater in the S-812217 group than in the placebo group at all time points except at Day 36 for core score, and at Day 36 and Day 43 for insomnia symptoms score. The differences in adjusted means between the intervention groups (S-812217 – placebo) were nominally significant ($p < 0.05$) for core score at Day 3, anxiety score at Day 3 and Day 8, Bech-6 score at Day 3 and Day 8, Maier score at Day 3 and Day 8, and insomnia symptoms score at Day 3, Day 8, and Day 15.
- The Kaplan-Meier estimate of median (95% CI) time from baseline to the first achievement of a HAM-D17 total score ≤ 13, censored when a participant discontinued, completed, or had a re-treatment, was 55.0 (34.0, not estimated) days in the S-812217 group and not estimable in the placebo group (stratified log-rank test, $p = 0.2622$). The Kaplan-Meier estimate of median (95% CI) time from baseline to the first achievement of a HAM-D17 total score ≤ 13, censored when a participant discontinued or completed, was 55.0 (34.0, 65.0) days in the S-812217 group and 63.0 (41.0, 66.0) days in the placebo group (stratified log-rank test, $p = 0.4675$).

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- The improvement rate in CGI-I score was higher in the S-812217 group than in the placebo group at all time points except at Day 36. The adjusted odds ratio (95% CI) were 4.55 (1.28, 16.16) at Day 3 and 2.74 (1.47, 5.09) at Day 8 with the S-812217 group achieving nominal significance versus placebo ($p < 0.05$).
- The improvement rate in CGI-S score was higher in the S-812217 group than in the placebo group at all time points except at Day 3. The adjusted odds ratio (95% CI) was 2.48 (1.21, 5.09) at Day 29 with the S-812217 group achieving nominal significance versus placebo ($p < 0.05$).
- The adjusted mean changes from baseline in CGI-S score were greater in the S-812217 group than in the placebo group at all time points, with nominal significance ($p < 0.05$) at Day 3 and Day 8.
- The improvement rate in PGI-I score was higher in the S-812217 group than in the placebo group at all time points except at Day 22. The adjusted odds ratio (95% CI) was 9.22 (1.16, 73.19) at Day 3 with the S-812217 group achieving nominal significance versus placebo ($p < 0.05$).
- The adjusted mean changes from baseline in PHQ-9 total score were greater in the S-812217 group than in the placebo group at Day 8, Day 50, and Day 57.
- The adjusted mean changes from baseline in SF-36 mental component summary score at Day 36 and vitality score at Day 57 were greater in the S-812217 group than in the placebo group, with nominal significance ($p < 0.05$). Otherwise, there were no notable differences between the intervention groups in summary scores or any domain scores at any time point of Part A.
- The adjusted mean changes from baseline in ISI total score were greater in the S-812217 group than in the placebo group at all time points, with nominal significance ($p < 0.05$) at Day 3, Day 8, Day 15, and Day 50.
- The Kaplan-Meier estimate of median (95% CI) time from the last dose of Part A in the treatment period to the start of a re-treatment, censored when a participant discontinued or completed, was 45.0 (44.0, 45.0) days in the S-812217/S-812217 group and 44.0 (not estimated, not estimated) days in the placebo/S-812217 group (stratified log-rank test, $p = 0.1530$).

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- Among the participants who proceeded to Part B, the percentage of those who needed a re-treatment in Part B was 89.0% (129/145) in the S-812217/S-812217 group and 89.5% (145/162) in the placebo/S-812217 group.

Subgroup analysis

Greater changes from baseline in HAM-D17 total score in the S-812217 group compared with the placebo group were consistently observed in all the subgroups examined, which confirms the robustness of the primary analysis result.

Part B

- For the participants with 1-year follow-up from their first treatment of S-812217, the number of treatment cycles of S-812217 including the treatment in Part A was 1 in 19 participants (13 participants [13.7%] in the S-812217/S-812217 group and 6 participants [6.7%] in the placebo/S-812217 group, hereinafter in the same order), 2 in 16 participants (11 participants [11.6%] and 5 participants [5.6%]), 3 in 17 participants (10 participants [10.5%] and 7 participants [7.9%]), 4 in 17 participants (8 participants [8.4%] and 9 participants [10.1%]), 5 in 14 participants (6 participants [6.3%] and 8 participants [9.0%]), 6 in 64 participants (10 participants [10.5%] and 54 participants [60.7%]), and 7 in 37 participants (37 participants [38.9%] and 0 participants). Participants in the placebo/S-812217 group could not receive 7 cycles of treatment with S-812217 due to the study design (ie, the number of treatment cycles in Part B was 6 at the maximum).
- In all treatment cycles of Part B, the mean of HAM-D17 total score was decreased from the cycle baseline at all time points in both intervention groups. In the S-812217/S-812217 group, the mean (SD) change at Day 15 from the cycle baseline in HAM-D17 total score was −5.3 (4.8) in Cycle 1, −4.9 (4.9) in Cycle 2, −4.1 (4.4) in Cycle 3, −4.4 (4.5) in Cycle 4, −4.2 (4.2) in Cycle 5, and −3.6 (3.7) in Cycle 6. In the placebo/S-812217 group, the mean (SD) change at Day 15 from the cycle baseline in HAM-D17 total score was −4.8 (4.8) in Cycle 1, −5.4 (4.6) in Cycle 2, −5.0 (4.4) in Cycle 3, −4.5 (4.8) in Cycle 4, −4.8 (5.2) in Cycle 5, and −4.5 (4.5) in Cycle 6.
- The response rate in HAM-D17 total score at Day 15 in the S-812217/S-812217 group was 16.5% (20/121) in Cycle 1, 19.8% (19/96) in Cycle 2, 18.9% (14/74) in Cycle 3, 20.0% (12/60) in Cycle 4, 17.3% (9/52) in

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Cycle 5, and 7.3% (3/41) in Cycle 6. The response rate in HAM-D17 total score at Day 15 in the placebo/S-812217 group was 16.7% (21/126) in Cycle 1, 20.2% (21/104) in Cycle 2, 20.2% (18/89) in Cycle 3, 18.1% (15/83) in Cycle 4, 20.6% (13/63) in Cycle 5, and 20.4% (11/54) in Cycle 6.

- The remission rate in HAM-D17 total score at Day 15 in the S-812217/S-812217 group was 14.0% (17/121) in Cycle 1, 15.6% (15/96) in Cycle 2, 12.2% (9/74) in Cycle 3, 18.3% (11/60) in Cycle 4, 17.3% (9/52) in Cycle 5, and 4.9% (2/41) in Cycle 6. The remission rate in HAM-D17 total score at Day 15 in the placebo/S-812217 group was 11.1% (14/126) in Cycle 1, 11.5% (12/104) in Cycle 2, 9.0% (8/89) in Cycle 3, 9.6% (8/83) in Cycle 4, 9.5% (6/63) in Cycle 5, and 5.6% (3/54) in Cycle 6.
- In all treatment cycles of Part B, the means of all HAM-D17 subscale scores on a percentage scale were decreased from the cycle baselines at all time points in both intervention groups, except Day 57 in Cycle 5 in the S-812217/S-812217 group for the insomnia symptoms score.
- The Kaplan-Meier estimate of median (95% CI) time from the last dose in the treatment period of each treatment cycle to a re-treatment in the S-812217/S-812217 group was 45.0 (44.0, 45.0) days in Cycle 1, 44.0 (44.0, 45.0) days in Cycle 2, 44.0 (44.0, 45.0) days in Cycle 3, 44.0 (not estimated, not estimated) days in Cycle 4, and 44.0 (44.0, 45.0) days in Cycle 5. The Kaplan-Meier estimate of median (95% CI) time from the last dose in the treatment period of each treatment cycle to a re-treatment in the placebo/S-812217 group was 45.0 (44.0, 45.0) days in Cycle 1, 45.0 (44.0, 46.0) days in Cycle 2, 44.0 (44.0, 45.0) days in Cycle 3, 44.0 (44.0, 45.0) days in Cycle 4, and 44.0 (not estimated, not estimated) days in Cycle 5.
- The Kaplan-Meier estimate of median (95% CI) time from baseline to the first response in HAM-D17 total score in the S-812217/S-812217 group was 169.0 (64.0, not estimated) days in Cycle 1, 85.0 (85.0, not estimated) days in Cycle 2, 197.0 (197.0, not estimated) days in Cycle 3, 86.0 (67.0, not estimated) days in Cycle 5, 85.0 (85.0, not estimated) days in Cycle 6, and not estimable in Cycle 4. The Kaplan-Meier estimate of median (95% CI) time from baseline to the first response in HAM-D17 total score in the placebo/S-812217 group was 144.0 (111.0, 232.0) days in Cycle 1, 83.0 (81.0, not estimated) days in Cycle 2, 141.0 (141.0, not estimated) days in Cycle 3,

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93.0 (not estimated, not estimated) days in Cycle 6, and not estimable in Cycle 4 and Cycle 5.

- The Kaplan-Meier estimate of median (95% CI) time from baseline to the first remission in HAM-D17 total score in the S-812217/S-812217 group was 87.0 (73.0, not estimated) days in Cycle 1, 85.0 (84.0, not estimated) days in Cycle 2, 197.0 (197.0, not estimated) days in Cycle 3, 85.0 (59.0, not estimated) days in Cycle 4, 86.0 (67.0, not estimated) days in Cycle 5, and 85.0 (85.0, not estimated) days in Cycle 6. The Kaplan-Meier estimate of median (95% CI) time from baseline to the first remission in HAM-D17 total score in the placebo/S-812217 group was 144.0 (111.0, not estimated) days in Cycle 1, 86.0 (85.0, not estimated) days in Cycle 2, and not estimable in Cycles 3 to 6.
- The improvement rate in CGI-I score at Day 15 in the S-812217/S-812217 group was 27.3% (33/121) in Cycle 1, 29.2% (28/96) in Cycle 2, 29.7% (22/74) in Cycle 3, 27.9% (17/61) in Cycle 4, 30.8% (16/52) in Cycle 5, and 26.8% (11/41) in Cycle 6. The improvement rate in CGI-I score at Day 15 in the placebo/S-812217 group was 30.2% (38/126) in Cycle 1, 29.8% (31/104) in Cycle 2, 33.7% (30/89) in Cycle 3, 26.5% (22/83) in Cycle 4, 36.5% (23/63) in Cycle 5, and 31.5% (17/54) in Cycle 6.
- The improvement rate in CGI-S score at Day 15 in the S-812217/S-812217 group was 9.9% (12/121) in Cycle 1, 15.6% (15/96) in Cycle 2, 8.1% (6/74) in Cycle 3, 14.8% (9/61) in Cycle 4, 15.4% (8/52) in Cycle 5, and 4.9% (2/41) in Cycle 6. The improvement rate in CGI-S score at Day 15 in the placebo/S-812217 group was 7.1% (9/126) in Cycle 1, 12.5% (13/104) in Cycle 2, 9.0% (8/89) in Cycle 3, 13.3% (11/83) in Cycle 4, 12.7% (8/63) in Cycle 5, and 13.0% (7/54) in Cycle 6.
- The improvement rate in PGI-I score at Day 15 in the S-812217/S-812217 group was 20.6% (26/126) in Cycle 1, 15.3% (15/98) in Cycle 2, 13.2% (10/76) in Cycle 3, 16.4% (10/61) in Cycle 4, 22.2% (12/54) in Cycle 5, and 14.0% (6/43) in Cycle 6. The improvement rate in PGI-I score at Day 15 in the placebo/S-812217 group was 18.5% (25/135) in Cycle 1, 16.4% (18/110) in Cycle 2, 19.1% (18/94) in Cycle 3, 16.7% (14/84) in Cycle 4, 11.9% (8/67) in Cycle 5, and 16.1% (9/56) in Cycle 6.

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- In all treatment cycles of Part B, the mean of PHQ-9 total score was decreased from the cycle baseline at all time points in both intervention groups. The mean (SD) change from baseline in PHQ-9 total score at Day 15 in the S-812217/S-812217 group was −3.2 (4.6) in Cycle 1, −3.0 (5.3) in Cycle 2, −2.3 (4.4) in Cycle 3, −3.6 (5.1) in Cycle 4, −3.7 (4.5) in Cycle 5, and −2.7 (5.3) in Cycle 6. The mean (SD) change from baseline in PHQ-9 total score at Day 15 in the placebo/S-812217 group was −3.2 (4.5) in Cycle 1, −3.1 (4.9) in Cycle 2, −3.0 (4.9) in Cycle 3, −2.9 (4.5) in Cycle 4, −3.9 (5.3) in Cycle 5, and −3.6 (4.4) in Cycle 6.
- There were no notable changes with repeated cycles in summary scores or any of the 8 domain scores of SF-36 at baselines in either intervention group. In all treatment cycles of Part B, the means of summary scores and 8 domain scores of SF-36 at Day 15 were increased from cycle baselines in both intervention groups, except Cycle 3 in the S-812217/S-812217 group and Cycle 5 in the placebo/S-812217 group for physical component summary score.
- In all treatment cycles of Part B, the mean of ISI total score was decreased from the cycle baseline at all time points in both intervention groups, except Day 57 of Cycle 5 in the S-812217/S-812217 group. The mean (SD) change from baseline in ISI total score at Day 15 in the S-812217/S-812217 group was −4.4 (5.9) in Cycle 1, −4.3 (5.5) in Cycle 2, −4.1 (5.8) in Cycle 3, −4.3 (5.9) in Cycle 4, −4.4 (5.8) in Cycle 5, and −3.7 (6.5) in Cycle 6. The mean (SD) change from baseline in ISI total score at Day 15 in the placebo/S-812217 group was −3.6 (4.8) in Cycle 1, −3.8 (4.5) in Cycle 2, −3.9 (4.9) in Cycle 3, −3.2 (5.1) in Cycle 4, −3.7 (5.1) in Cycle 5, and −3.3 (4.3) in Cycle 6.

Safety:

Part A

- Of the 412 randomized participants, 404 (205 in the S-812217 group and 199 in the placebo group) were included in the safety analysis set of Part A.
- The incidences of TEAEs and treatment-related AEs in the S-812217 group were higher than those in the placebo group; 217 TEAEs were reported in 113 of 205 participants (55.1%) of the S-812217 group, while 121 TEAEs were reported in 81 of 199 participants (40.7%) of the placebo group. A total of 108 treatment-related AEs were reported in 70 of 205 participants (34.1%) of

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the S-812217 group, while 34 treatment-related AEs were reported in 24 of 199 participants (12.1%) of the placebo group.

- Treatment-emergent AEs occurring with an incidence of 5% or greater in the S-812217 group were somnolence (13.2%), dizziness (12.7%), and feeling abnormal (6.3%), while that in the placebo group was somnolence (6.0%).
- All TEAEs were mild or moderate in severity.
- Most of the TEAEs reported in Part A were resolved or resolving. Of the TEAEs reported in the treatment period, 1 event in the S-812217 group and 2 events in the placebo group were not resolved. Of the TEAEs reported in the follow-up period, 2 events in the S-812217 group and 4 events in the placebo group were not resolved. All treatment-related AEs reported in Part A were resolved or resolving.
- No pharmacological or pathological TEAEs of interest were reported in either intervention group.
- Neither death nor nonfatal serious TEAE was reported in Part A.
- A total of 5 TEAEs led to discontinuation of study intervention in 2 participants (1.0%) of the S-812217 group (2 events of dizziness, 1 event each of headache, nausea, and malaise). All of them were considered related to the study intervention, moderate in severity, and resolved.
- A total of 6 special situations were reported in 4 participants of the S-812217 group. More specifically, 1 misuse was reported in 1 participant, 3 overdoses were reported in 2 participants, and 2 medication errors were reported in 2 participants. No special situations were reported in the placebo group.
- No apparent trends over time related to S-812217 treatment were identified in laboratory parameters, vital signs, body weight, 12-lead ECG, or other safety observations.
- No notable between-group differences were observed in the results of C-SSRS assessments.
- There were no participants with any TEAE suggesting dependence on or abuse of the study intervention or withdrawal symptoms.

Part B

- Of the 307 participants who proceeded to Part B, 271 participants (128 in the S-812217/S-812217 group and 143 in the placebo/S-812217 group, hereinafter

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in the same order) were included in the safety analysis set at Cycle 1, 213 (99 and 114) were included in the safety analysis set at Cycle 2, 170 (76 and 94) were included in the safety analysis set at Cycle 3, 147 (63 and 84) were included in the safety analysis set at Cycle 4, 126 (55 and 71) were included in the safety analysis set at Cycle 5, and 99 (43 and 56) were included in the safety analysis set at Cycle 6. Of the 307 participants who proceeded to Part B, 163 participants (74 and 89) were included in the 1-year Followed Up population.

- A total of 807 TEAEs were reported in 228 of 304 participants (75.0%) over the entire study population; 372 TEAEs were reported in 110 of 144 participants (76.4%) of the S-812217/S-812217 group, while 435 TEAEs were reported in 118 of 160 participants (73.8%) of the placebo/S-812217 group. A total of 235 treatment-related AEs were reported in 103 of 304 participants (33.9%) over the entire study population; 126 treatment-related AEs were reported in 52 of 144 participants (36.1%) of the S-812217/S-812217 group, while 109 treatment-related AEs were reported in 51 of 160 participants (31.9%) of the placebo/S-812217 group. The incidence of TEAEs did not increase in association with repeated cycles.
- Treatment-emergent AEs occurring with an incidence of 5% or greater for the entire study over the entire study population were nasopharyngitis (15.8%), somnolence (15.1%), COVID-19 (14.5%), dizziness (10.2%), pyrexia (10.2%), back pain (6.3%), headache (5.9%), and feeling abnormal (5.3%). Treatment-emergent AEs occurring with an incidence of 5% or greater were nasopharyngitis (18.1%), somnolence (15.3%), COVID-19 (12.5%), dizziness (10.4%), pyrexia (10.4%), feeling abnormal (6.9%), nausea (6.3%), and headache (5.6%) in the S-812217/S-812217 group, and COVID-19 (16.3%), somnolence (15.0%), nasopharyngitis (13.8%), dizziness (10.0%), pyrexia (10.0%), back pain (7.5%), headache (6.3%), and diarrhoea (5.6%) in the placebo/S-812217 group.
- During the treatment period in Part B, 1 severe TEAE was reported in 1 participant (0.8%) of the S-812217/S-812217 group in Cycle 1, and 2 severe TEAEs were reported in 2 participants (1.8%) of the placebo/S-812217 group in Cycle 2. During the follow-up period in Part B, 1 severe TEAE was reported in 1 participant (0.9%) of the placebo/S-812217 group in Cycle 2, and 1 severe TEAE was reported in 1 participant (1.4%) of the placebo/S-812217

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group in Cycle 5. All other TEAEs reported in Part B were categorized as moderate or mild.

- Most of the TEAEs reported in Part B were resolved or resolving. All treatment-related AEs reported in Part B were resolved or resolving except for 2 events whose outcome were unknown because of lost to follow-up.
- A pharmacological or pathological TEAE of interest (sedation) was reported in 1 of 94 participants (1.1%) of the placebo/S-812217 group in Cycle 3.
- No deaths were reported in Part B.
- A total of 4 nonfatal serious TEAEs (1 event each of altered state of consciousness, large intestine polyp, cerebral infarction, and vertigo positional) were reported in 3 participants (2.1%) of the S-812217/S-812217 group, while 6 nonfatal serious TEAEs (1 event each of COVID-19, liver function test abnormal, mechanical ileus, pneumothorax spontaneous, malignant pleural effusion, and invasive ductal breast carcinoma) were reported in 3 participants (1.9%) of the placebo/S-812217 group. Two of the serious TEAEs were considered related to the study intervention: altered state of consciousness reported in 1 participant (0.7%) of the S-812217/S-812217 group and liver function test abnormal reported in 1 participant (0.6%) of the placebo/S-812217 group. Five of the serious TEAEs were severe in severity; 4 serious TEAEs were moderate and 1 serious TEAE was mild in severity. One of the serious TEAEs was not resolved; all other serious TEAEs were resolved or resolving.
- A total of 4 TEAEs led to discontinuation of study intervention in 2 participants (1.4%) of the S-812217/S-812217 group (1 event each of headache, dizziness, malaise, and altered state of consciousness), while 7 TEAEs led to discontinuation of study intervention in 6 participants (3.8%) of the placebo/S-812217 group (1 event each of liver function test abnormal, feeling drunk, akathisia, palpitations, nausea, dizziness, and somnolence). All of them were considered related to the study intervention. Two of the TEAEs leading to discontinuation of study intervention were severe in severity; all other TEAEs were mild or moderate in severity. All TEAEs leading to discontinuation of study intervention were resolved or resolving.
- A total of 4 special situations were reported in 4 participants of the S-812217/S-812217 group and 4 special situations were reported in 4 participants of the placebo/S-812217 group. More specifically, 3 misuses by

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participants' self-judgement of not taking study intervention or non-continuous use of study intervention were reported in 3 participants (2 of the S-812217/S-812217 group and 1 of the placebo/S-812217 group), 1 overdose was reported in 1 participant of the S-812217/S-812217 group, and 4 medication errors were reported in 4 participants (1 of the S-812217/S-812217 group and 3 of the placebo/S-812217 group).

- One participant of the placebo/S-812217 group met the liver chemistry stopping criteria in Cycle 2. This abnormality was reported as a serious TEAE (liver function test abnormal).
- No apparent trends over time related to S-812217 treatment were identified in laboratory parameters, vital signs, body weight, 12-lead ECG, or other safety observations.
- No notable trends over time were observed in either intervention group in the results of C-SSRS assessments.
- There were no participants with any TEAE suggesting dependence on or abuse of the study intervention or withdrawal symptoms.

CONCLUSIONS

Overall, statistically significant improvement in the primary endpoint was found in the S-812217 group compared with the placebo group. For some secondary endpoints of Part A, nominally significant changes were seen in widely accepted measures for participant with depression in the S-812217 group compared with the placebo group. Of 184 participants with 1-year follow-up from their first treatment of S-812217, 28% received 1-3 cycles, 17% received 4-5 cycles and 55% received 6-7 cycles. Trends toward improvement with re-treatment of S-812217 were observed for the efficacy endpoints in Part B over up to 1-year follow-up. Changes in symptoms of depression were consistent among up to seven 14-day treatment cycles in this study. S-812217 was generally safe and well tolerated in this study. The safety profiles (TEAE incidence, type, and severity) were consistent across multiple (up to 7) 14-day treatment cycles in this study.

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