2. SYNOPSIS

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

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

Investigators and Study Centers: This study was a multicenter study conducted at 24 sites in Japan.

Publication (reference): Not applicable

Studied Period:
From 26 Nov 2022 to 21 Mar 2024 (last participant last observation in Part B)

Phase of Development: Phase 3

Objectives and Endpoints:

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

<table>
<tr><td>Sponsor:
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<tr><td>Name of Finished Product
Not applicable</td><td>Volume:</td><td></td></tr>
<tr><td>Name of Active Ingredient:
S-812217</td><td colspan="2">Page:</td></tr>
<tr><td></td><td colspan="2">Presence or absence of remission[c] by HAM-D17 total score at each time point
Days from baseline[b] to the first remission[c] by HAM-D17 total score
Changes from baseline[b] in HAM-D17 subscale scores at each time point
Changes from baseline[b] in individual HAM-D17 scores at each time point
Days from baseline[b] 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[b] 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[b] in PHQ-9 total score at each time point
Changes from baseline[b] in individual PHQ-9 scores at each time point
Change from baseline[b] in ISI total score at each time point</td></tr>
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	• Changes from baseline[b] in individual ISI scores at each time point
• To evaluate the safety and tolerability of an add-on treatment with S-812217 for 14 days in comparison with placebo in Japanese participants with depression taking an antidepressant.	• AEs, blood pressure and pulse rate, 12-lead ECG, laboratory tests, C-SSRS, D-2-A, D-2-B, and DEQ-5
• To evaluate the number of participants who needed add-on re-treatment with S-812217 and the number of days from the last dose in the treatment period to re-treatment in Japanese participants with depression taking an antidepressant.	• Presence or absence of re-treatment • Days from the last dose in the treatment period to re-treatment
• To confirm the PK of S-812217 administered as an add-on treatment in Japanese participants with depression taking an antidepressant.	• Plasma S-812217 concentration
Part B	
• To evaluate the safety and tolerability of an add-on re-treatment with S-812217 in Japanese participants with depression taking an antidepressant.	• AEs, blood pressure and pulse rate, 12-lead ECG, laboratory tests, C-SSRS, D-2-A, D-2-B, and DEQ-5
• To evaluate the number of add-on re-treatment cycles of S-812217 (performed after the first treatment cycle) during half-year (26 weeks) follow-up in Japanese participants with depression taking an antidepressant.	• Number of add-on treatment cycles of S-812217 for each participant (including treatment in Part A)

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

• To evaluate the efficacy of an add-on re-treatment with S-812217 in Japanese participants with depression taking an antidepressant.	• HAM-D17 total score and its change from baseline[d] at each time point • Presence or absence of response[a] by HAM-D17 total score at each time point • Presence or absence of remission[c] by HAM-D17 total score at each time point • HAM-D17 subscale scores and their changes from baseline[d] at each time point • Individual HAM-D17 scores and their changes from baseline[d] at each time point • Days from the last dose in the treatment period of each treatment cycle to re-treatment • Days from baseline[d] to the first response[a] 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 total score and its change from baseline[d] at each time point • Individual PHQ-9 scores and their changes from baseline[d] at each time point

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

	• ISI total score and its change from baseline[d] at each time point • Individual ISI scores and their changes from baseline[d] at each time point
• To confirm the PK of S-812217 administered as an add-on re-treatment in Japanese participants with depression taking an antidepressant.	• Plasma S-812217 concentration
Exploratory	
• To evaluate the effect of S-812217 as an add-on treatment on sleep in Japanese participants with depression taking an antidepressant.	• Sleep diary endpoints

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

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

b Baseline in Part A was defined as Visit 1 (Day 1).

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

d Baseline in Part B was defined as 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 taking an antidepressant. 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 5 weeks), a treatment period (2 weeks), and a follow-up period (6 weeks), with the total study duration of 9 to 13 weeks. On Day 1 to Day 14 during the treatment period, participants received S-812217 or placebo once

daily in addition to an antidepressant that they had taken for more than 4 weeks prior to Visit 1 (Day 1) of Part A.

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 to 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.

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. Participants 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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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

Number of Participants (Planned and Analyzed):

Planned:

Part A: The target number of randomized participants was 100 in total (50 each in the S-812217 and placebo groups).

Part B: No target sample size was specified.

Part A:

Randomized: 108 (55 in the S-812217 group, 53 in the placebo group)

Analyzed for efficacy:

- Full analysis set (FAS):
  107 (55 in the S-812217 group, 52 in the placebo group)
- Per protocol set (PPS):
  103 (51 in the S-812217 group, 52 in the placebo group)

Analyzed for safety:

- Safety analysis set:
  107 (55 in the S-812217 group, 52 in the placebo group)

Analyzed for pharmacokinetics (PK):

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

Part B

Analyzed for efficacy:

- FAS:
  Cycle 1
  76 (44 in the S-812217/S-812217 group, 32 in the placebo/S-812217 group)
  Cycle 2
  61 (36 in the S-812217/S-812217 group, 25 in the placebo/S-812217 group)
  Cycle 3
  45 (26 in the S-812217/S-812217 group, 19 in the placebo/S-812217 group)
  Cycle 4
  34 (19 in the S-812217/S-812217 group, 15 in the placebo/S-812217 group)
  Cycle 5
  20 (11 in the S-812217/S-812217 group, 9 in the placebo/S-812217 group)
  Cycle 6
  14 (7 in the S-812217/S-812217 group, 7 in the placebo/S-812217 group)

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

Analyzed for safety:

- Safety analysis set:
  Cycle 1
  76 (44 in the S-812217/S-812217 group, 32 in the placebo/S-812217 group)
  Cycle 2
  61 (36 in the S-812217/S-812217 group, 25 in the placebo/S-812217 group)
  Cycle 3
  45 (26 in the S-812217/S-812217 group, 19 in the placebo/S-812217 group)
  Cycle 4
  34 (19 in the S-812217/S-812217 group, 15 in the placebo/S-812217 group)
  Cycle 5
  20 (11 in the S-812217/S-812217 group, 9 in the placebo/S-812217 group)
  Cycle 6
  14 (7 in the S-812217/S-812217 group, 7 in the placebo/S-812217 group)
- Half-year Followed Up population
  49 (30 in the S-812217/S-812217 group, 19 in the placebo/S-812217 group)

Analyzed for PK:

- PK Concentration population:
  Cycle 1
  76 (44 in the S-812217/S-812217 group, 32 in the placebo/S-812217 group)
  Cycle 2
  61 (36 in the S-812217/S-812217 group, 25 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 who had been taking 1 antidepressant (any one of selective serotonin reuptake inhibitors [SSRIs], serotonin noradrenaline reuptake inhibitors [SNRIs], or serotonin reuptake inhibitors and serotonin receptor modulators) for more than 4 weeks prior to Visit 1 (Day 1) (without any change in dosage and administration).
- Patients with a HAM-D17 total score of ≥ 14 at Visit pre and Day 1.
- Patients with a Patient Health Questionnaire-9 (PHQ-9) total score of ≥ 10 at Visit pre and 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.
- 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 within the approved dose range 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 with a ≥ 50% decrease in HAM-D17 total score between Visit pre and 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.

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

- 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
- 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 Part B due to unresolved adverse events (AEs) from Part A.
- Patients who had changed, discontinued, or changed the dosage or administration of the concomitant antidepressant that had been taken since the informed consent for Part B.
- 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:
  - Patients who answered "Yes" in Part A 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.

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.

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

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:

Primary Endpoint (Part A)

The primary endpoint was analyzed on the FAS. The supplementary analyses were performed on the PPS.

Inverse probability weighted-generalized estimating equation (IPW-GEE) was applied to the between-group comparison of the presence or absence of response by HAM-D17 total score defined as a reduction by ≥ 50% from baseline HAM-D17 total score at Visit 4 (Day 15 ± 1) of Part A, the primary endpoint, using as an index the odds ratio of the S-812217 group to the placebo group for response rate which was the summary statistic by study intervention group. All available data from Day 3 ± 1 through Day 57 ± 2 were analyzed using IPW-GEE which included the presence or absence of response by HAM-D17 total score as the response variable, intervention group, time point, and interaction between the intervention group and time point as fixed effects, and sex and baseline HAM-D17 total score (≤ 19 vs ≥ 20) as covariates. Each visit was weighted with the inverse of the propensity score, which represented the conditional observation probability of the response up to that visit. IPW-GEE assumed an independent structure for the working correlation matrix.

Secondary Endpoint (Part A)

The secondary endpoints were analyzed on the FAS.

Of continuous endpoints, the changes from baseline were compared between the S-812217 and placebo groups at each visit using the mixed effect model for repeated measures (MMRM). All available data at each visit were analyzed using MMRM which included 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 and sex as covariates. The MMRM did not assume a specific covariance structure for error term.

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

For discrete 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 IPW-GEE. All available data at each visit were analyzed using 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 and sex as covariates.

Kaplan-Meier curves were presented for each intervention group and compared between the groups 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. In addition, summary statistics were calculated by presence or absence of 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 add-on 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 the evaluation of at least half year after the initial dose in Part B.
- HAM-D17 total score and its change from baseline at each time point
  Summary statistics were calculated by time point 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 the presence or absence of response by HAM-D17 total score, the number and percentage of participants were calculated by time point in each treatment cycle.
- Presence or absence of remission by HAM-D17 total score at each time point
  For the presence or absence of remission by HAM-D17 total score, the number and percentage of participants were calculated by time point in each treatment cycle.

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

- HAM-D17 subscale scores and their changes from baseline at each time point
  Summary statistics were calculated by time point for HAM-D17 subscale scores and their changes from the start of study intervention in each treatment cycle.
- Individual HAM-D17 scores and their changes from baseline at each time point
  Summary statistics were calculated by time point for individual HAM-D17 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 the presence or absence of improvement in CGI-I score, the number and percentage of participants were calculated by time point in each treatment cycle. In addition, summary statistics were calculated by time point for CGI-I score.
- Clinical global impression - severity of illness (CGI-S) score and presence or absence of its improvement at each time point
  For the presence or absence of improvement in CGI-S score, the number and percentage of participants were calculated by time point in each treatment cycle. In addition, summary statistics by time point were calculated for CGI-S score and its change from the start of study intervention in each treatment cycle.

- Patient global impression of improvement (PGI-I) score and presence or absence of its improvement at each time point
  For the presence or absence of improvement in PGI-I score, the number and percentage of participants were calculated by time point in each treatment cycle. In addition, summary statistics by time point were calculated for PGI-I scores.
- PHQ-9 total score and its change from baseline at each time point
  For PHQ-9 total score and its change from the start of study intervention in each treatment cycle, the summary statistics were calculated by time point.
- Individual PHQ-9 scores and their changes from baseline at each time point
  For individual PHQ-9 scores and their changes from the start of study intervention in each treatment cycle, the summary statistics were calculated by 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 by time point.
- Individual ISI scores and their changes from baseline at each time point
  For individual ISI scores and their changes from the start of study intervention in each treatment cycle, the summary statistics were calculated by 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 was 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 by 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 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 efficacy of an add-on treatment with S-812217 in participants using an antidepressant for at least 4 weeks was not demonstrated with respect to the primary endpoint, ie, the response rate in HAM-D17 total score at Day 15, for the FAS; the response rate in HAM-D17 total score at Day 15 was 13.2% (7/53) in the S-812217 group and 21.6% (11/51) in the placebo group, and the adjusted odds ratio (95% CI) at Day 15 was 0.56 (0.20, 1.59) ($p = 0.2791$). The result of primary endpoint analysis in the PPS was consistent with that in the FAS; the adjusted odds ratio (95% CI) at Day 15 was 0.62 (0.22, 1.75) ($p = 0.3637$).

Secondary Endpoints

Part A

- The adjusted mean changes from baseline in HAM-D17 total score were smaller in the S-812217 group than in the placebo group at all time points.
- The response rate in HAM-D17 total score was lower in the S-812217 group than in the placebo group at all time points.
- 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 222.0 (115.0, not estimated) days in the S-812217 group and 239.0 (43.0, not estimated) days in the placebo group (stratified log-rank test, $p = 0.7248$).

Sponsor: Shionogi & Co., Ltd.	**Individual Study Table** **Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

- The remission rate in HAM-D17 total score was lower in the S-812217 group than in the placebo group at all time points.
- 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 was 310.0 (175.0, not estimated) days in the S-812217 group and 372.0 (78.0, not estimated) days in the placebo group (stratified log-rank test, p = 0.5788).
- For the HAM-D17 insomnia symptoms subscale score 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 Day 50 and Day 57. For other HAM-D17 subscale scores on a percentage scale, the adjusted mean changes from baseline were smaller in the S-812217 group than in the placebo group at all time points.
- 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 not estimable in the S-812217 group and 36.0 (16.0, not estimated) days in the placebo group (stratified log-rank test, p = 0.4556). 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 64.0 (15.0, 71.0) days in the S-812217 group and 36.0 (16.0, 92.0) days in the placebo group (stratified log-rank test, p = 0.6857).
- The improvement rate in CGI-I score was lower in the S-812217 group than in the placebo group at all time points.
- The improvement rate in CGI-S score was lower in the S-812217 group than in the placebo group at all time points.
- The adjusted mean changes from baseline in CGI-S score were smaller in the S-812217 group than in the placebo group at all time points.
- The improvement rate in PGI-I score was higher in the S-812217 group than in the placebo group at Day 15, Day 22, and Day 29.
- The adjusted mean changes from baseline in PHQ-9 total score in the S-812217 group were smaller than in the placebo group at all time points.

- The adjusted mean changes from baseline in the PHQ-9 score for trouble falling or staying asleep were greater in the S-812217 group than in the placebo group at Day 3, Day 8, and Day 15. The adjusted mean changes (decreases) from baseline in the PHQ-9 score were smaller in the S-812217 group than in the placebo group at all time points for trouble concentrating on things and for thoughts you be better off dead. Otherwise, there were no notable differences in the changes in any individual PHQ-9 scores between the S-812217 group and the placebo group.
- The adjusted mean changes from baseline in ISI total score were greater in the S-812217 group than in the placebo group at Day 3, Day 8, and Day 15, and were smaller in the S-812217 group than in the placebo group at Day 22 and onwards.
- Among the participants who proceeded to Part B, the percentage of those who needed a re-treatment in Part B was 93.6% (44/47) in the S-812217/S-812217 group and 91.4% (32/35) in the placebo/S-812217 group.
- 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 was 44.0 (44.0, 45.0) days in the S-812217/S-812217 group and 45.0 (44.0, 47.0) days in the placebo/S-812217 group (stratified log-rank test, $p = 0.1748$).

Part B

- For the participants with half-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 3 participants (0 participants [0%] in the S-812217/S-812217 group and 3 participants [15.8%] in the placebo/S-812217 group, hereinafter in the same order), 2 in 8 participants (7 participants [23.3%] and 1 participant [5.3%]), 3 in 9 participants (6 participants [20.0%] and 3 participants [15.8%]), 4 in 29 participants (17 participants [56.7%] and 12 participants [63.2%]).
- 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, except Day 57 of Cycle 5 in the placebo/S-812217 group. In the S-812217/S-812217 group, the mean (SD) change at Day 15 from the cycle baseline in HAM-D17 total score was −3.7 (4.6) in Cycle 1, −3.2 (3.7) in Cycle 2, −4.0 (3.2) in Cycle 3, −4.3 (4.2) in Cycle 4, −2.7 (2.0) in Cycle 5, and −2.3 (2.4) 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 −3.6 (5.1) in

Cycle 1, −5.3 (6.3) in Cycle 2, −4.8 (6.2) in Cycle 3, −3.5 (3.7) in Cycle 4, −3.2 (3.2) in Cycle 5, and −4.7 (3.9) in Cycle 6.

- The response rate in HAM-D17 total score at Day 15 in the S-812217/S-812217 group was 11.6% (5/43) in Cycle 1, 8.3% (3/36) in Cycle 2, 7.7% (2/26) in Cycle 3, 11.1% (2/18) in Cycle 4, 0% (0/11) in Cycle 5, and 0% (0/7) in Cycle 6. The response rate in HAM-D17 total score at Day 15 in the placebo/S-812217 group was 9.7% (3/31) in Cycle 1, 21.7% (5/23) in Cycle 2, 15.8% (3/19) in Cycle 3, 6.7% (1/15) in Cycle 4, 0% (0/9) in Cycle 5, and 14.3% (1/7) in Cycle 6.
- The remission rate in HAM-D17 total score at Day 15 in the S-812217/S-812217 group was 7.0% (3/43) in Cycle 1, 5.6% (2/36) in Cycle 2, 0% (0/26) in Cycle 3, 11.1% (2/18) in Cycle 4, 0% (0/11) in Cycle 5, and 0% (0/7) in Cycle 6. The remission rate in HAM-D17 total score at Day 15 in the placebo/S-812217 group was 3.2% (1/31) in Cycle 1, 17.4% (4/23) in Cycle 2, 10.5% (2/19) in Cycle 3, 6.7% (1/15) in Cycle 4, 0% (0/9) in Cycle 5, and 14.3% (1/7) in Cycle 6.
- In all treatment cycles of Part B, the means of all HAM-D17 subscale scores at Day 15 on a percentage scale were decreased from the cycle baselines in both intervention groups.
- The Kaplan-Meier estimate of median (95% CI) time from the last dose in the treatment period to a re-treatment in the S-812217/S-812217 group was 44.0 (not estimated, not estimated) days in Cycle 1, 45.0 (44.0, 54.0) 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, 63.0) days in Cycle 5. The Kaplan-Meier estimate of median (95% CI) time from the last dose in the treatment period to a re-treatment in the placebo/S-812217 group was 45.0 (44.0, 51.0) days in Cycle 1, 44.0 (44.0, 50.0) days in Cycle 2, 44.0 (44.0, 46.0) days in Cycle 3, 44.0 (42.0, 46.0) days in Cycle 4, and 45.0 (43.0, 46.0) 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 86.0 (not estimated, not estimated) days in Cycle 4, and not estimable in Cycles 1 to 3, Cycle 5, and Cycle 6. 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 96.0 (96.0, not estimated) days in Cycle 1, 87.0 (not estimated, not estimated) days in Cycle 2, 85.0 (58.0, not estimated) days in Cycle 3, not estimable in Cycles 4 to 6.

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

- 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 83.0 (58.0, not estimated) days in Cycle 1, 86.0 (not estimated, not estimated) days in Cycle 4, and not estimable in Cycle 2, Cycle 3, Cycle 5, and 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 148.0 (96.0, not estimated) days in Cycle 1, 87.0 (not estimated, not estimated) days in Cycle 2, 85.0 (58.0, not estimated) days in Cycle 3, not estimable in Cycles 4 to 6.
- The improvement rate in CGI-I score at Day 15 in the S-812217/S-812217 group was 18.6% (8/43) in Cycle 1, 16.7% (6/36) in Cycle 2, 19.2% (5/26) in Cycle 3, 22.2% (4/18) in Cycle 4, 18.2% (2/11) in Cycle 5, and 42.9% (3/7) in Cycle 6. The improvement rate in CGI-I score at Day 15 in the placebo/S-812217 group was 22.6% (7/31) in Cycle 1, 21.7% (5/23) in Cycle 2, 21.1% (4/19) in Cycle 3, 20.0% (3/15) in Cycle 4, 11.1% (1/9) in Cycle 5, and 28.6% (2/7) in Cycle 6.
- The improvement rate in CGI-S score at Day 15 in the S-812217/S-812217 group was 4.7% (2/43) in Cycle 1, 8.3% (3/36) in Cycle 2, 3.8% (1/26) in Cycle 3, 5.6% (1/18) in Cycle 4, 0.0% (0/11) in Cycle 5, and 0.0% (0/7) in Cycle 6. The improvement rate in CGI-S score at Day 15 in the placebo/S-812217 group was 6.5% (2/31) in Cycle 1, 17.4% (4/23) in Cycle 2, 10.5% (2/19) in Cycle 3, 6.7% (1/15) in Cycle 4, 0.0% (0/9) in Cycle 5, and 0.0% (0/7) in Cycle 6.
- The improvement rate in PGI-I score at Day 15 in the S-812217/S-812217 group was 14.0% (6/43) in Cycle 1, 2.8% (1/36) in Cycle 2, 11.5% (3/26) in Cycle 3, 21.1% (4/19) in Cycle 4, 18.2% (2/11) in Cycle 5, and 14.3% (1/7) in Cycle 6. The improvement rate in PGI-I score at Day 15 in the placebo/S-812217 group was 16.1% (5/31) in Cycle 1, 21.7% (5/23) in Cycle 2, 10.5% (2/19) in Cycle 3, 13.3% (2/15) in Cycle 4, 33.3% (3/9) in Cycle 5, and 14.3% (1/7) in Cycle 6.

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	

- The mean (SD) change from baseline in PHQ-9 total score at Day 15 in the S-812217/S-812217 group was −2.1 (4.6) in Cycle 1, −2.2 (4.1) in Cycle 2, −3.0 (3.8) in Cycle 3, −3.7 (4.9) in Cycle 4, −1.8 (2.2) in Cycle 5, and −2.4 (4.2) in Cycle 6. The mean (SD) change from baseline in PHQ-9 total score at Day 15 in the placebo/S-812217 group was −1.9 (4.3) in Cycle 1, −2.8 (3.3) in Cycle 2, −1.3 (3.9) in Cycle 3, −1.1 (2.8) in Cycle 4, −1.8 (2.3) in Cycle 5, and −1.3 (1.7) in Cycle 6.
- The mean (SD) change from baseline in ISI total score at Day 15 in the S-812217/S-812217 group was −3.2 (5.2) in Cycle 1, −3.1 (4.9) in Cycle 2, −4.5 (5.1) in Cycle 3, −5.2 (4.9) in Cycle 4, −3.5 (3.3) in Cycle 5, and −5.7 (4.7) in Cycle 6. The mean (SD) change from baseline in ISI total score at Day 15 in the placebo/S-812217 group was −2.9 (3.5) in Cycle 1, −4.3 (5.2) in Cycle 2, −5.5 (5.8) in Cycle 3, −2.8 (3.1) in Cycle 4, −4.1 (5.3) in Cycle 5, and −4.1 (6.3) in Cycle 6.

Safety:

Part A

- Of the 108 randomized participants, 107 (55 in the S-812217 group and 52 in the placebo group) were included in the safety analysis set of Part A.
- The overall incidences of TEAEs and treatment-related AEs in the S-812217 group were higher than those in the placebo group; 63 TEAEs were reported in 37 of 55 participants (67.3%) of the S-812217 group, while 41 TEAEs were reported in 22 of 52 participants (42.3%) of the placebo group. A total of 30 treatment-related AEs were reported in 23 of 55 participants (41.8%) of the S-812217 group, while 8 treatment-related AEs were reported in 6 of 52 participants (11.5%) of the placebo group. The overall incidences of TEAEs and treatment-related AEs were similar across the categories of concomitant antidepressant.
- Treatment-emergent AEs occurring with an incidence of 5% or greater in the S-812217 group were somnolence (20.0%), nausea (12.7%), and nasopharyngitis and dizziness (7.3% each), while those in the placebo group were back pain (7.7%) and insomnia (5.8%).
- All TEAEs were mild or moderate in severity.

- Most of the TEAEs were resolved or resolving. Of the TEAEs reported in the treatment period, 1 event in the S-812217 group was not resolved. Of the TEAEs reported in the follow-up period, 4 events in the S-812217 group and 4 events in the placebo group were not resolved. All treatment-related AEs were resolved.
- No pharmacological or pathological TEAEs of interest were reported in either intervention group.
- No deaths were reported.
- One nonfatal serious TEAE (hepatic function abnormal) was reported in 1 participant (1.9%) of the placebo group. This event was considered related to the study intervention, mild in severity, and resolved. No nonfatal serious TEAEs were reported in the S-812217 group.
- One TEAE (asthenia) led to discontinuation of study intervention in 1 participant (1.8%) of the S-812217 group. This event was considered related to the study intervention, moderate in severity, and resolved. No TEAEs leading to discontinuation of study intervention were reported in the placebo group.
- No special situations were reported.
- One participant of the placebo group met the liver chemistry stopping criteria. This abnormality was reported as a serious TEAE (hepatic function 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 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 82 participants who proceeded to Part B, no participants were excluded from the safety analysis set at any cycle of Part B: 76 participants (44 in the S-812217/S-812217 group and 32 in the placebo/S-812217 group, hereinafter in the same order) were included in the safety analysis set at Cycle 1, 61 (36 and 25) were included in the safety analysis set at Cycle 2, 45 (26 and 19) were included in the safety analysis set at Cycle 3, 34 (19 and 15) were included in the safety analysis set at Cycle 4, 20 (11 and 9) were included in the safety

analysis set at Cycle 5, and 14 (7 and 7) were included in the safety analysis set at Cycle 6. Of the 82 participants who proceeded to Part B, 49 participants (30 and 19) were included in the Half-year Followed Up population.

- A total of 227 TEAEs were reported in 66 of 82 participants (80.5%) over the entire study population: 119 TEAEs were reported in 38 of 47 participants (80.9%) of the S-812217/S-812217 group, while 108 TEAEs were reported in 28 of 35 participants (80.0%) of the placebo/S-812217 group. A total of 54 treatment-related AEs were reported in 17 of 82 participants (20.7%) over the entire study population: 24 treatment-related AEs were reported in 9 of 47 participants (19.1%) of the S-812217/S-812217 group, while 30 treatment-related AEs were reported in 8 of 35 participants (22.9%) 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 (30.5%), somnolence (12.2%), COVID-19 (11.0%), dizziness (9.8%), influenza (7.3%), and headache (6.1%). Treatment-emergent AEs occurring with an incidence of 5% or greater for the entire study in the S-812217/S-812217 group were nasopharyngitis (25.5%), COVID-19 and somnolence (10.6% each), influenza, sinusitis, dizziness, headache, nausea, and vomiting (6.4% each), while those in the placebo/S-812217 group were nasopharyngitis (37.1%), somnolence and dizziness (14.3% each), COVID-19 (11.4%), influenza, back pain, and pyrexia (8.6% each), cystitis, aggression, headache, hypertension, diarrhoea, thirst, blood creatine phosphokinase increased, and weight increased (5.7% each).
- All TEAEs were mild or moderate in severity.
- Most of the TEAEs were resolved or resolving. All treatment-related AEs were resolved or resolving.
- Pharmacological or pathological TEAEs of interest were reported in 1 participant each in Cycle 2, Cycle 3, and Cycle 4 in the S-812217/S-812217 group. All the pharmacological or pathological TEAEs of interest were sedation and reported in the same participant.
- No deaths were reported.

- One nonfatal serious TEAE (hepatic function abnormal) was reported in 1 participant (2.1%) of the S-812217/S-812217 group. This event was considered not related to the study intervention, moderate in severity, and resolved. No nonfatal serious TEAEs were reported in the placebo/S-812217 group.
- A total of 3 TEAEs (1 event each of insomnia, dizziness, and hepatic function abnormal) led to discontinuation of study intervention in 3 participants (6.4%) of the S-812217/S-812217 group, while 1 TEAE (dizziness) led to discontinuation of study intervention in 1 participant (2.9%) of the placebo/S-812217 group. All of them except a TEAE of hepatic function abnormal were considered related to the study intervention. All TEAEs leading to discontinuation of study intervention were mild or moderate in severity, and resolved or resolving.
- A total of 3 special situations were reported in 3 participants of the S-812217/S-812217 group and 1 special situation was reported in 1 participant of the placebo/S-812217 group. All special situations were misuses by participants' self-judgment or mistake.
- One participant of the S-812217/S-812217 group met the liver chemistry stopping criteria in Cycle 2. This abnormality was reported as a serious TEAE (hepatic function 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

No statistically significant improvement in the primary endpoint was found in the add-on S-812217 group compared with the add-on placebo group in patients who were taking an antidepressant for at least 4 weeks. In Part A, efficacy of S-812217 for participants with depression was suggested in some of the secondary endpoints concerning sleep, with nominally significant changes compared with the placebo group. There were no notable trends over time for any secondary endpoint in either

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Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: S-812217	**Page:**	
intervention group in Part B. S-812217 was generally safe and well tolerated in this study as an add-on treatment to an antidepressant.		
Date of Report: 19 Aug 2024		