Summary of Clinical Study Results for General Audience
Plain Language Summary

1. STUDY NAME

A phase 3 study of S-812217 in patients with major depressive disorder

2. WHO SPONSORED THIS STUDY?

This study was sponsored by Shionogi & Co., Ltd.

3. GENERAL INFORMATION ABOUT THIS STUDY

Depression is an illness associated with depressed mood and loss of emotions of interest or joy. In some cases, individuals may also experience reduced sleep, loss of body weight or reduced appetite, or difficulties with thinking and memory, and even want to die or attempt suicide. In Japan, the percentage of people who experience depression at least once in their lifetime is estimated to be approximately 6%; and the probability of relapse or recurrence is reported to be approximately 50%. If depression symptoms become stronger again when they have not been completely cured, this is called a “relapse,” and if the symptoms reappear after completely disappearing, this is called a “recurrence.” The initial occurrence of the symptoms (initial episode) is often triggered by high stress, but it is reported that, in relapse/recurrence, unlike the initial episode, symptoms often occur without an obvious cause.

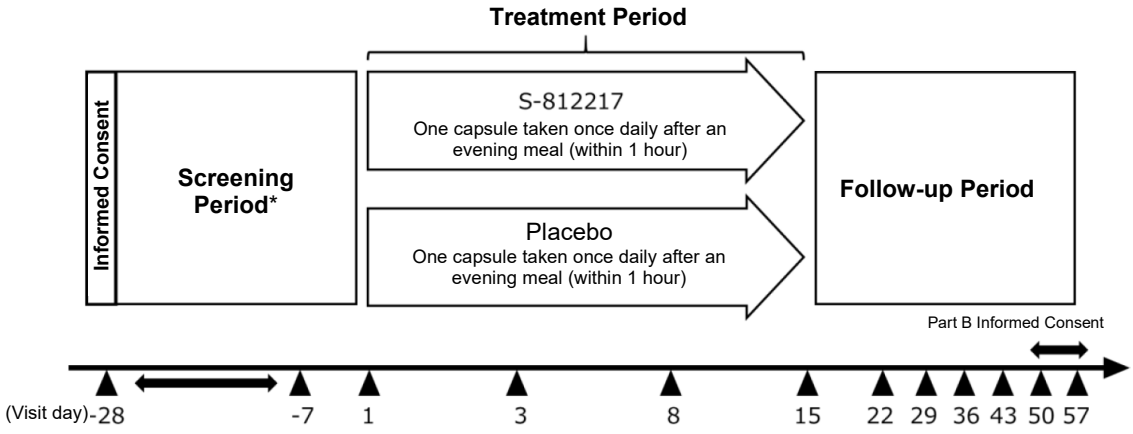
Some patients do not get enough benefit from the medicines (antidepressants). In addition, antidepressants can take a long time to begin working, and the dose often needs to be adjusted gradually by a doctor. There is still no treatment for depression that satisfies all patients, and new medications are desired. S-812217 is being developed with the aim of providing a drug with a high level of satisfaction among depression patients.

This study is called a phase 3 study. This phase 3 study consisted of 2 parts, Part A and Part B. In Part A, about 400 patients participated, and in Part B, about 300 patients participated. The study confirmed the effectiveness and safety of the drug. The pharmacokinetics when S-812217 is taken were also investigated. Pharmacokinetics is a record of how a drug is absorbed into the body, appears in the blood, and then disappears over time.

The effect of S-812217 was assessed using the 17-item Hamilton Depression Rating Scale (hereinafter referred to as “HAM-D17”) to assess the severity of depression symptoms. Using the HAM-D17, a doctor assesses the severity of 17 items, including depressed mood, feelings of guilt, poor concentration, anxiety and tension, and higher total scores indicate more severe depression symptoms.

The schedule of activities in Part A is shown in Figure 1. Part A consisted of 3 periods, a screening period (1 to 4 weeks), a treatment period (2 weeks), and a follow-up period (6 weeks). During the screening period, the tests were done to determine if patients could participate in the study. If they were eligible to participate, during the treatment period, patients took either a capsule containing 30 mg of the active ingredient S-812217 or a dummy capsule (hereinafter referred to as "placebo") that looks like S-812217 but does not contain any active ingredients. During the follow-up period, patients did not take the drug, and their depression symptoms and physical condition were investigated. The main purpose of Part A was to investigate how much depression symptoms improved relative to before the drugs were taken, compared to placebo.

Figure 1 Schedule of Activities in Part A



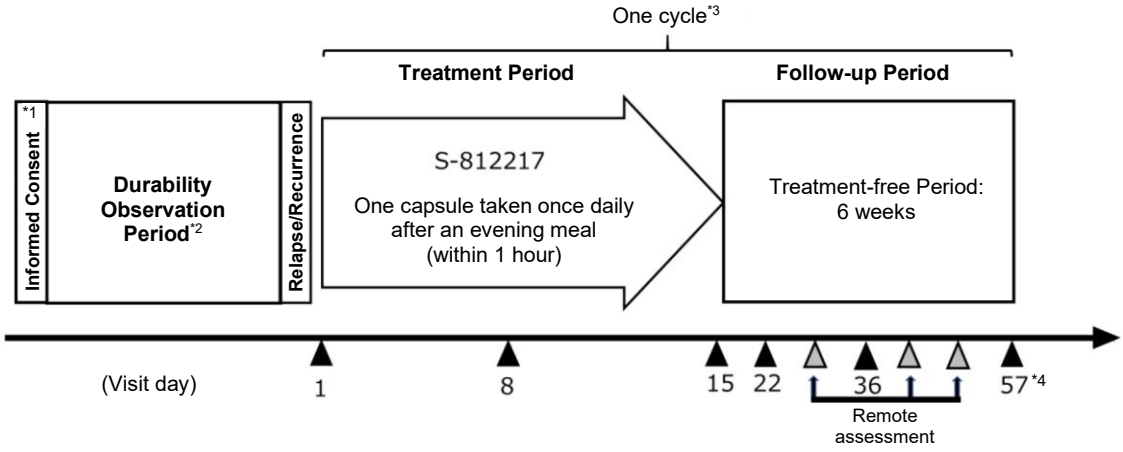
* During the screening period, the tests were done to determine if patients could participate in the study. The implementation period was from 28 days to 7 days before the patients received their first dose of S-812217 or placebo.

In Part B, patients who had completed Part A and whose depression symptoms met the criteria for starting a treatment period were able to take S-812217 again. The schedule of activities in Part B is shown in Figure 2. Part B consisted of 3 periods, a durability observation period, a treatment period (2 weeks), and a follow-up period (6 weeks). The durability observation period was a period for checking whether the effects received from the drug were continuing, and patients moved on to the durability observation period if their depression symptoms were stable at the end of the follow-up period in Part A or Part B.

If depression symptoms met the criteria for starting the treatment period at the end of the follow-up period or during the durability observation period, patients were able to move on to the treatment period. One cycle consisted of a treatment period and a follow-up period, and up to 6 cycles were performed. The duration of Part B was 1 year (52 weeks) from the first dose of Part B when patients moved on the treatment period, and was 1 year (52 weeks) from the start of treatment in Part A when they did not move on the treatment period.

In Part A, about half of the patients took placebo, but in Part B, all patients whose depression symptoms met the criteria for starting the treatment period took S-812217, and the safety, drug effect, and pharmacokinetics of S-812217 were investigated.

Figure 2 Schedule of Activities in Part B



*1 Patients who agreed to participate in Part B signed the informed consent form during their Part A visit from day 50 ± 2 to day 57 ± 2.

*2 If patients met the criteria for starting the treatment period based on their depression symptoms, they moved on to the treatment period; otherwise, they moved on to the durability observation period.

*3 One cycle consisted of a treatment period + a follow-up period, and up to 6 cycles were performed.

*4 At visit day 57 ± 2, based on the HAM-D17 total score and duration of depression symptoms, whether patients met the criteria for starting the treatment period of Part B was checked. If a patient met the criteria, that patient moved on to the treatment period within 1 week, and if the patient did not meet the criteria, the patient moved on to the durability observation period.

This study was conducted in Japan from February 2022 to May 2024.

4. WHAT PATIENTS WERE INCLUDED IN THIS STUDY?

Patients who had a diagnosis of depression according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5), that is the guideline for mental health diagnosis from the American Psychiatric Association, participated in Part A. Patients whose depression symptoms before starting the study had continued for at least 8 weeks and less than 1 year, and whose depression symptoms were moderate to severe, were included. Moderate to severe depression symptoms were defined as a HAM-D17 total score of 22 or higher and a total score of 15 or higher for PHQ-9, which is a 9-item questionnaire about the patient's health. For the PHQ-9 questionnaire, patients themselves answer 9 questions about depression, and a higher total score based on these answers indicates more severe depression. Japanese male or female patients aged 18 to 75 years at the time of giving informed consent, who were visiting as outpatients, were eligible to participate.

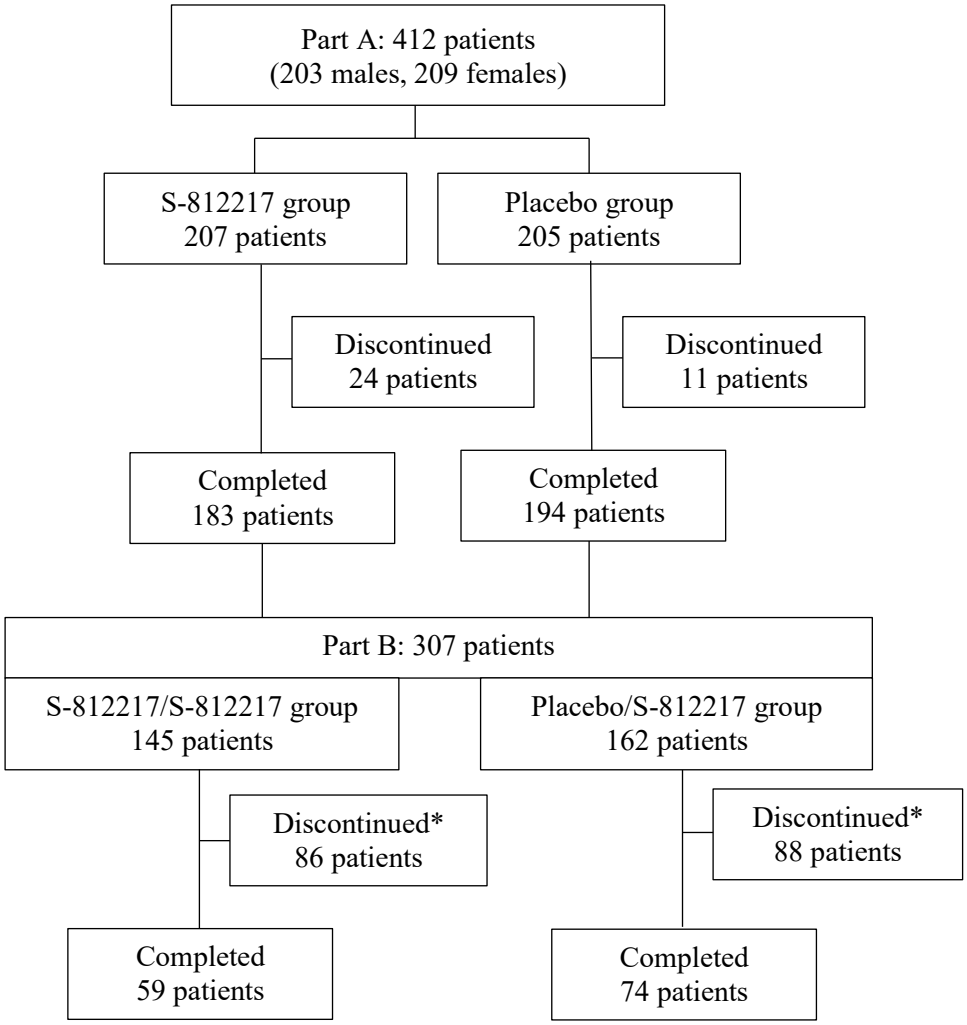
Part A was a "double-blinded" study. That means that neither the patients nor the study doctors knew who received S-812217 and who received a placebo during this study. This approach ensures that the study results are unbiased and fair. Patients in this study were randomly assigned to one of these groups taking either S-812217 or the placebo to reduce bias between the groups.

The disposition of participants in this study is shown in Figure 3.

In Part A, 412 Japanese depression patients (203 males and 209 females) participated. Of these, 207 patients were assigned to the group taking S-812217 (hereinafter referred to as the "S-812217 group") and 205 patients were assigned to the group taking the placebo (hereinafter referred to as the "placebo group"). Of the 207 patients in the S-812217 group, 183 patients completed Part A and 24 patients were prematurely discontinued during Part A. Of the 205 patients in the placebo group, 194 patients completed Part A and 11 patients were prematurely discontinued during Part A. The common reasons for premature discontinuation during Part A were lack of the drug effect (8 patients in the S-812217 group and 2 patients in the placebo group) and request for withdrawal by the patient (5 patients in the S-812217 group and 4 patients in the placebo group).

Out of all patients who completed Part A, 307 patients participated in Part B. Of the 307 patients who participated in Part B, 145 patients had been assigned to the S-812217 group in Part A (hereinafter referred to as the "S-812217/S-812217 group") and 162 patients had been assigned to the placebo group in Part A (hereinafter referred to as the "placebo/S-812217 group"). Sixteen of the 145 patients in the S-812217/S-812217 group and 17 of the 162 patients in the placebo/S-812217 did not take S-812217. Of the 145 patients in the S-812217/S-812217 group, 59 patients completed Part B and 86 patients were prematurely discontinued during Part B. Of the 162 patients in the placebo/S-812217 group, 74 patients completed Part B and 88 patients were prematurely discontinued during Part B. The common reason for premature discontinuation during Part B was request for withdrawal by the patient (33 patients in the S-812217/S-812217 group and 29 patients in the placebo/S-812217 group). Because the number of treatment cycles was 6 at the maximum, in Cycle 6, 30 patients in the S-812217/S-812217 group and 31 patients in the placebo/S-812217 group who could not complete the 52-week study period of Part B were discontinued from the study.

Figure 3 Disposition of Participants in the Study



* Includes the following patients:

Patients who did not take the drug (S-812217/S-812217 group: 16 patients, placebo/S-812217 group: 17 patients).

Patients who could not complete the 52-week period of Part B because the number of treatment cycles was 6 at the maximum (as of Cycle 6, S-812217/S-812217 group: 30 patients, placebo/S-812217 group: 31 patients).

5. WHICH STUDY DRUGS WERE STUDIED?

The study drugs used in this study are S-812217 (active drug) and placebo (a substance with no active ingredients).

The patients who participated in Part A took capsules containing 30 mg of S-812217 or placebo once daily for 14 days (treatment period) after an evening meal (Figure 1). In Part A, 207 patients took S-812217 at least once, and 203 patients took placebo at least once.

The patients who participated in Part B took capsules containing 30 mg of S-812217 once daily for 14 days (treatment period) after an evening meal, and then stopped taking the capsules for 6 weeks (follow-up period). At the end of the follow-up period, if their depression symptoms met the criteria for starting the treatment period, they moved on to the treatment period again. If symptoms were stable, they moved on to the durability observation period, and if, during this period, their depression symptoms met the criteria for starting the treatment period, they moved on to the treatment period again. One cycle consisted of a 14-day treatment period and a 6-week follow-up period, and up to 6 cycles were performed (Figure 2). In Part B, 274 patients took S-812217 at least once.

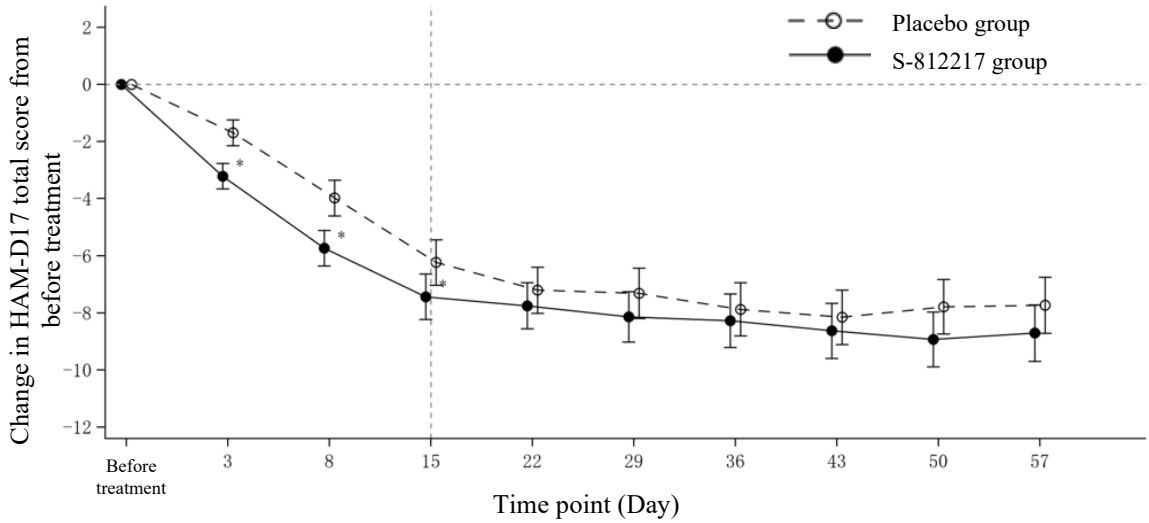
6. WHAT WERE THE OVERALL RESULTS OF THIS STUDY?

In this section, primary endpoint and secondary endpoints are mentioned.

In Part A, the average HAM-D17 total score before the drug was taken (higher scores indicate more severe depression symptoms) was 24.1 points in both the S-812217 group and the placebo group, and there was no difference between groups.

The change over time in HAM-D17 total score before the drug was taken in Part A is shown in Figure 4. The HAM-D17 total score after 2 weeks of taking the drug (Day 15) decreased by 7.43 points in the S-812217 group and decreased by 6.23 points in the placebo group compared to before the drug was taken. This means that the change in HAM-D17 total score after 2 weeks of taking the drug (Day 15) was 1.20 points lower in the S-812217 group than in the placebo group, showing the result that S-812217 improved depression symptoms with statistical significance compared with placebo.

Figure 4 **Change over Time in HAM-D17 Total Score from Before Treatment in Part A**



* Time points at which depression symptoms improved with statistical significance in the S-812217 group compared with the placebo group

In Part B, in all cycles, regardless of whether the patient had taken S-812217 or placebo in Part A, the average HAM-D17 total score decreased after S-812217 was taken, compared to before S-812217 was taken on Day 1 of each cycle.

7. WHAT WERE THE SIDE EFFECTS?

A lot of research is needed to know whether a drug causes medical problems. So, when new drugs are being studied, researchers keep track of all unwanted symptoms that patients have while they are in this study.

- A “side effect” means any unwanted symptom that is judged by the study doctor to be possibly caused by a study drug used in the study.
- A “serious side effect” means a side effect possibly caused by a study drug that is considered “serious” when it results in death, is life-threatening, causes lasting problems, needs hospital care, causes birth problems or is other medically important state.

Table 1 shows the side effects experienced by 5 or more patients in the S-812217 group and placebo group combined, among the patients who participated in Part A. The most common side effect was somnolence, followed by dizziness, feeling abnormal, nausea and headache.

Table 2 shows the side effects experienced by 5 or more patients in the S-812217/S-812217 group and placebo/S-812217 group combined for each cycle, among the patients who participated in Part B. Of the side effects reported in 5 or more patients from Cycles 1 to 5, the most common side effect was dizziness, followed by somnolence, feeling abnormal, headache and nausea.

In Part A, no patients experienced serious side effects. In Part B, the serious side effects experienced were loss of consciousness in 1 patient in the S-812217/S-812217 group and increase in the blood levels of certain enzymes produced by the liver in 1 patient in the placebo/S-812217 group. No patients experienced clinically significant abnormal findings in laboratory tests, blood pressure, pulse rate, 12-lead electrocardiogram or other physical examination results in either part.

Table 1 Side Effects Experienced by a Total of 5 or More Patients Among the 2 Groups in Part A

Side Effect	Number of Patients	
	S-812217 group (out of 205 patients) [1)]	Placebo group (out of 199 patients) [2)]
Somnolence	27 (13.2%)	11 (5.5%)
Dizziness	26 (12.7%)	2 (1.0%)
Feeling abnormal	13 (6.3%)	1 (0.5%)
Nausea	6 (2.9%)	2 (1.0%)
Headache	4 (2.0%)	3 (1.5%)

1) Side effects were assessed in 205 patients in Part A, from among the 207 patients assigned to the S-812217 group, with 2 patients excluded from assessment of side effects. One patient was excluded due to violations of the regulations to be followed when conducting clinical studies (clinical trials) of drugs, and another patient was excluded because no safety information was obtained after the drug was taken.

2) Side effects were assessed in 199 patients in Part A, from among the 205 patients assigned to the placebo group, with 6 patients excluded from assessment of side effects because they had violations from the regulations to be followed when conducting clinical studies (clinical trials) of drugs, because they did not take the drug, or because no safety information was obtained after the drug was taken.

Somnolence: A state where you quickly fall asleep but wake up if spoken to or tapped lightly

Dizziness: Feeling lightheaded

Feeling abnormal: A state where you feel physically unwell or changed

Nausea: Feeling queasy

Table 2 Side Effects Experienced by a Total of 5 or More Patients Among the 2 Groups in Part B

Cycle 1		
Side Effect	S-812217/S-812217 group (out of 128 patients) [1)]	Placebo/S-812217 group (out of 143 patients) [1)]
Somnolence	14 (10.9%)	18 (12.6%)
Dizziness	13 (10.2%)	10 (7.0%)
Feeling abnormal	4 (3.1%)	4 (2.8%)
Headache	3 (2.3%)	4 (2.8%)
Nausea	3 (2.3%)	3 (2.1%)
Cycle 2		
Side Effect	S-812217/S-812217 group (out of 99 patients) [1)]	Placebo/S-812217 group (out of 114 patients) [1)]
Somnolence	8 (8.1%)	3 (2.6%)
Dizziness	4 (4.0%)	3 (2.6%)
Feeling abnormal	3 (3.0%)	3 (2.6%)
Cycle 3		
Side Effect	S-812217/S-812217 group (out of 76 patients) [1)]	Placebo/S-812217 group (out of 94 patients) [1)]
Dizziness	3 (3.9%)	3 (3.2%)
Cycle 4		
Side Effect	S-812217/S-812217 group (out of 63 patients) [1)]	Placebo/S-812217 group (out of 84 patients) [1)]
Dizziness	2 (3.2%)	3 (3.6%)
Cycle 5		
Side Effect	S-812217/S-812217 group (out of 55 patients) [1)]	Placebo/S-812217 group (out of 71 patients) [1)]
Dizziness	2 (3.6%)	3 (4.2%)
Cycle 6		
	S-812217/S-812217 group (out of 43 patients) [1)]	Placebo/S-812217 group (out of 56 patients) [1)]
There were no side effects experienced by 5 or more patients.		

1) This shows the total number of patients whose side effects were assessed in each group per cycle.
Somnolence: A state where you quickly fall asleep but wake up if spoken to or tapped lightly
Dizziness: Feeling lightheaded
Feeling abnormal: A state where you feel physically unwell or changed
Nausea: Feeling queasy

8. HOW HAS THIS STUDY HELPED PATIENTS AND RESEARCHERS?

The results are limited to the particular patients and cannot be assumed to be true for everybody. Also, only the results of this study are included in this document. New information or different results about the study drug may be given in other studies. However, this research helps future patients and families by helping researchers understand more about the drug being studied.

9. ARE THERE PLANS FOR FURTHER STUDIES?

No other studies of S-812217 in patients with depression are currently ongoing or planned at this time.

10. WHERE CAN I FIND MORE INFORMATION ABOUT THIS STUDY?

You may find more information about this study:

Website	URL	Identifier
jRCT	Japanese: https://jrct.mhlw.go.jp/latest-detail/jRCT2031210577	number of clinical trial plan: jRCT2031210577

Contact information for the company that conducted this study:
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Shionogi & Co., Ltd.
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