Summary of Clinical Study Results for General Audience
Plain Language Summary

1. STUDY NAME

A phase 2 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

Major depressive disorder (also called depression; hereinafter referred to as depression) is an illness characterized by depressed mood and loss of interest or pleasure. Some people with depression also have sleeplessness, weight loss and poor appetite, and a decline in thinking power and memory. They sometimes want to die and attempt suicide. It is estimated that approximately 6% of Japanese people exhibit this illness at least once in their lifetime.

Some patients with depression do not sufficiently respond to treatment with currently available drugs (antidepressants). Additionally, long-term treatment is necessary because existing antidepressants may take time to have an effect and require dose adjustment (a physician needs to increase or decrease dose gradually). There is not yet any treatment for depression that satisfies the need of all patients with depression. Therefore, new therapeutic drugs are desired. S-812217 is under development to be an effective drug for patients with depression.

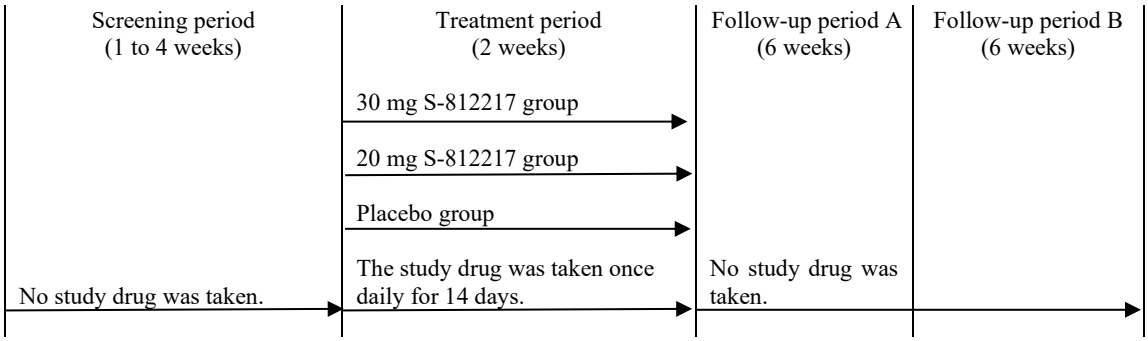
This study is called a Phase 2 study. A Phase 2 study is conducted to evaluate the effect (efficacy) and safety of the study drug and confirm how to use it in approximately 250 patients. The main purpose of this study was to compare two doses of S-812217 with placebo in terms of how much the symptoms of depression improved from before patients took the study drug. A placebo is a dummy drug that looks like S-812217 but does not contain any active ingredient. The safety and pharmacokinetics of S-812217 after patients took it were also evaluated. Pharmacokinetics is the change of a drug over time from its absorption in the body to its appearance and disappearance in the blood.

The efficacy of S-812217 was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D17), a method to assess the severity of depressive symptoms. In the HAM-D17, a physician assesses the severity of 17 items including depressed mood, feelings of guilt, a decline in concentration, anxiety, and nervous tension. A higher total score means a higher severity of depressive symptoms.

The study schedule is shown in Figure 1. The schedule of this study consisted of 4 periods: the screening period (1 to 4 weeks), treatment period (2 weeks), follow-up

period A (6 weeks), and follow-up period B (6 weeks). In the screening period, patients were examined to confirm whether they could participate in the study. In the treatment period, patients took 20 mg of S-812217, 30 mg of S-812217, or placebo once daily for 2 weeks. In the follow-up period A, patients did not take any study drug and were monitored for depressive symptoms and changes in their health conditions. In the follow-up period B, of the patients who had completed the follow-up period A, only those for whom further investigation was possible in the opinion of the investigator were monitored for depressive symptoms and change in their health conditions while they did not take any study drug.

Figure 1 Schematic study schedule



This study was conducted in Japan from June 2020 to September 2021.

4. WHAT PATIENTS WERE INCLUDED IN THIS STUDY?

This study enrolled patients who were diagnosed with major depressive disorder (depression) based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria. Patients could participate in this study when depressive symptoms had persisted for at least 8 weeks but less than 1 year before the start of the study and were classified as moderate or severe in severity. A patient was considered to have moderate or severe symptom severity when they have a HAM-D17 total score of ≥22 and a Patient Health Questionnaire-9 (PHQ-9) total score of ≥15. In the PHQ-9, patients self-assessed 9 items about depression. A higher total score calculated from a patient's response means a higher severity of depression.

This was a "double-blind" study. That means that neither the patients nor the investigators and physicians knew who received S-812217 and who received placebo during this study. This method is believed to make the study results fairer because it avoids possible bias. Patients in this study were assigned to take either of the study drugs or placebo randomly.

A total of 250 Japanese patients (106 males and 144 females) with depression took part in this study: 82 patients were in the group in which they took 30 mg of S-812217, 85 patients were in the group in which they took 20 mg of S-812217, and 83 patients were in the group in which they took placebo. In the treatment period, 10 patients (3 patients in the 30 mg S-812217 group, 4 patients in the 20 mg S-812217 group, and 3 patients in the placebo group) stopped study treatment. The main reason for stopping treatment was the patient's request.

5. WHICH DRUGS WERE STUDIED?

The study drugs used in this study are S-812217 capsules (10 mg of S-812217 per capsule) and placebo capsules. The drug type and the number of each capsule in each group are shown in Table 1. According to the drug type and the number of each capsule in Table 1, patients in each group took the study drugs within 1 hour after dinner once daily for 14 days.

Table 1 Drug type and the number of each capsule in each group

Group	Study drugs taken
30 mg S-812217 group	3 capsules of S-812217
20 mg S-812217 group	2 capsules of S-812217 and 1 capsule of placebo
Placebo group	3 capsules of placebo

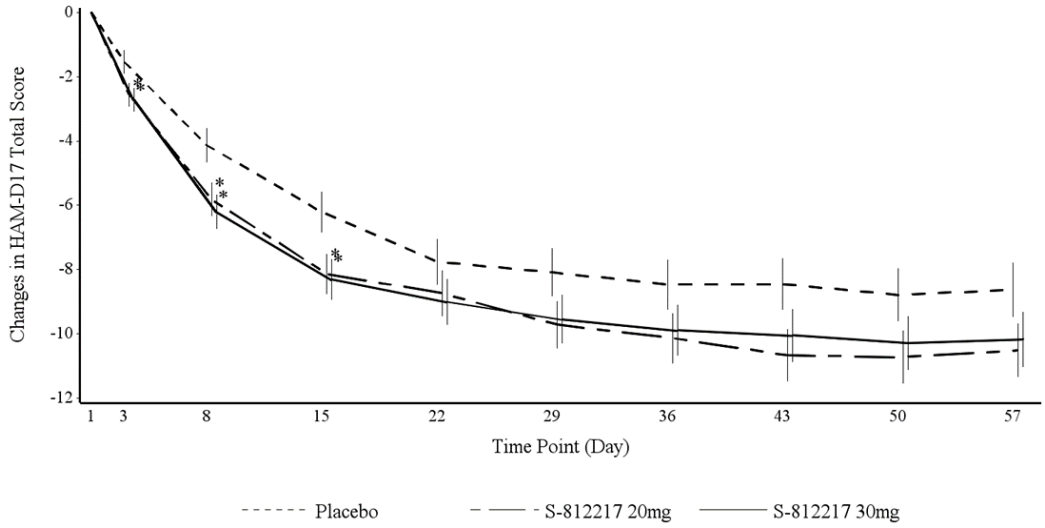
6. WHAT WERE THE OVERALL RESULTS OF THIS STUDY?

In this section, only the results of the primary endpoint are mentioned.

Before patients took the study drug, the mean HAM-D17 total score (a higher score means more severe depressive symptoms) was 24.6 in the 30 mg S-812217 group, 24.8 in the 20 mg S-812217 group, and 24.5 in the placebo group, which indicated no significant difference among these groups.

Changes over time in the HAM-D17 total score from before patients took the study drug are shown in Figure 2. After patients took the study drug for 2 weeks (at Day 15), the HAM-D17 total score was decreased by 8.31 in the 30 mg S-812217 group, 8.14 in the 20 mg S-812217 group, and 6.22 in the placebo group, when compared with that before they took the study drug. After patients took the study drug for 2 weeks (at Day 15), the HAM-D17 total score in the 30 mg S-812217 group was 2.09 lower than that in the placebo group and the HAM-D17 total score in the 20 mg S-812217 group was 1.92 lower than that in the placebo group, which indicated that 30 and 20 mg of S-812217 statistically significantly improved depressive symptoms compared with placebo.

Figure 2 Changes over time in the HAM-D17 total score from before patients took the study drug



* Time points at which the 30 mg S-812217 or 20 mg S-812217 group showed a statistically significant improvement in depressive symptoms compared with the placebo group

After patients took the study drug for 2 weeks (at Day 15), the proportion of patients in whom the HAM-D17 total score was reduced to ≤50% of that before they took the study drug was 31.3% (25 of 80 patients) in the 30 mg S-812217 group, 22.2% (18 of 81 patients) in the 20 mg S-812217 group, and 15.9% (13 of 82 patients) in the placebo group. It was higher in the 30 mg S-812217 and 20 mg S-812217 groups than in the placebo group.

After patients took the study drug for 2 weeks (at Day 15), the proportion of patients in whom the HAM-D17 total score was reduced to ≤7 (only very mild depressive symptoms remain) was 8.8% (7 of 80 patients) in the 30 mg S-812217 group, 9.9% (8 of 81 patients) in the 20 mg S-812217 group and 3.7% (3 of 82 patients) in the placebo group. It was higher in the 30 mg S-812217 and 20 mg S-812217 groups than in the placebo group.

7. WHAT WERE THE SIDE EFFECTS?

A lot of research is needed to know whether a drug causes a medical problem. Therefore, when new drugs are being developed, researchers keep track of all medical problems that patients have while they are in the clinical study. No single clinical study can give a complete picture of the risks of the study drug.

- A side effect means any medical problem that is judged by the investigators to have been possibly caused by the study drug used in a clinical study.
- A serious side effect means a side effect that results in death, is life threatening, causes permanent disability, needs hospitalization, consists of a congenital anomaly or birth defect, or is another medically important condition.

In this study, no patient experienced any serious side effect.

The table below shows the side effects experienced by 5 or more patients while taking part in this study.

Side Effect	Number of Patients with Side Effects		
	S-812217 30 mg (out of 82)	S-812217 20 mg (out of 85)	Placebo (out of 82)[1)]
Somnolence[2)]	17 (20.7%)	9 (10.6%)	3 (3.7%)
Dizziness	8 (9.8%)	8 (9.4%)	3 (3.7%)
Headache	1 (1.2%)	3 (3.5%)	3 (3.7%)
Constipation	2 (2.4%)	2 (2.4%)	1 (1.2%)

1) Of 83 patients assigned to the group in which they took placebo, one patient stopped participation in the study before taking placebo. Therefore, 82 patients took placebo.

2) Somnolence: a state in which a patient falls asleep instantly but wakes up if someone talks to or taps the patient.

8. HOW HAS THIS STUDY HELPED PATIENTS AND RESEARCHERS?

The results are limited to the patients of this particular study and cannot be assumed to be true for every patient. This research helps future patients and families by helping researchers understand more about this drug.

9. ARE THERE PLANS FOR FURTHER STUDIES?

As of September 2022, other studies of S-812217 in patients with depression are ongoing. These studies will collect more information about S-812217 and evaluate the effects and safety when S-812217 is used.

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

You may find more information about this study at the following Internet sites:

Website	URL	Identifier
jRCT	Japanese: https://jrct.mhlw.go.jp/latest-detail/jRCT2080225180	number of clinical trial plan: jRCT2080225180