Summary of Clinical Study Results for General Audience
Plain Language Summary

1. STUDY NAME

A phase 1b, parallel-group, observer-blind, 2-arm, 2-dose study to investigate the safety and tolerability of intravenous S-151128 compared with placebo in male and female participants aged 40 to 75 with knee osteoarthritis

2. WHO SPONSORED THIS STUDY?

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

3. GENERAL INFORMATION ABOUT THIS STUDY

Knee osteoarthritis is a disease where aging or prolonged stress causes the thinning of cartilage that serves as a cushion in the knee joint that then causes knee pain, and may lead to joint deformation as the disease progresses.

The treatment for knee osteoarthritis initially involves the use of analgesics, eliminating obesity, and strengthening the muscles around the knee with moderate exercise with less stress on the knee. If these treatments are not sufficiently effective, accumulated water will be drained from the joint in addition to the use of stronger analgesics, and hyaluronic acid, etc. will be directly injected into the joint. If inflammation is severe, steroids may be injected into the joint. Physical therapy, etc. are also performed to properly move the joint without putting much load on the knee.

If knee osteoarthritis progresses and the attending doctor deems it necessary, surgery, such as a procedure to cut the knee bone and adjust its position so that the joint comes into contact with the least damaged part of the bone (high tibial osteotomy) or a procedure to replace the joint with an artificial one made of ceramic and titanium (artificial joint replacement), is performed.

However, surgery can be a burden on the body, and rehabilitation is required after the surgery. Therefore, there is a need for treatment methods and therapeutic drugs that can be performed before the surgery which is associated with a huge burden, and are surely effective in treating the symptoms of knee osteoarthritis, particularly pain. In response to this need, S-151128, a drug (analgesic) that relieves pain with a new action, is being developed.

This study was called a phase 1b study and run in patients (males and females) with knee osteoarthritis. The purpose of this study was to evaluate the safety, effectiveness of the drug (efficacy), and pharmacokinetics of S-151128 using a dose that was found to be safe in a phase 1 study in healthy adults. Pharmacokinetics is the change of a drug over time from its absorption in the body to its appearance and disappearance in

the blood. Blood samples were taken at predetermined time points, and the concentration of S-151128 in blood was measured.

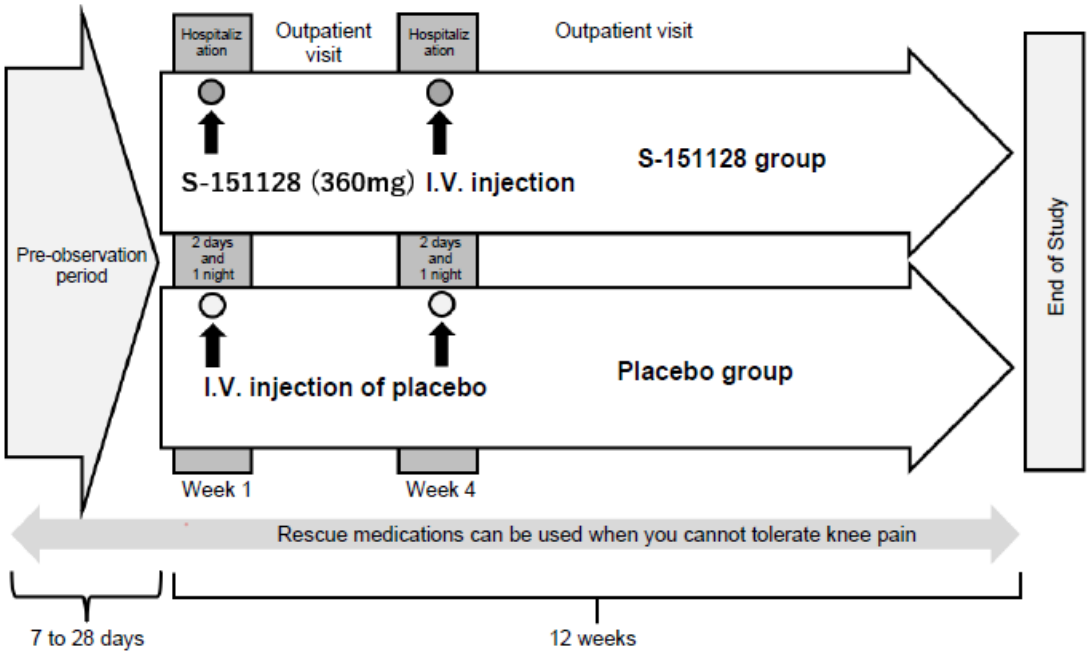
In terms of safety, observation of medical problems (adverse events) that happened in patients in the clinical study, laboratory tests (blood and urine), 12-lead electrocardiography, and imaging assessment (X-ray and MRI scan) of the knee joint were performed to confirm in total if patients experience undesirable effects from the study drug.

The effectiveness of the drug was evaluated using various questionnaires, etc. Among these, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which assesses the effects of knee pain on daily life, was used as the main indicator of the drug's effectiveness. The WOMAC consists of 24 questions, including pain (5 questions), stiffness (2 questions), and difficulty in daily activities (17 questions) in the past 48 hours, and patients rated each item on a scale from 0 to 10 points (a higher point indicates a worse condition).

An outline of the study schedule is shown in Figure 1. This study consisted of 2 periods: a preobservation period (7 to 28 days before the injection of the study drug) and a treatment period (12 weeks). In the preobservation period, whether or not patients could participate in this study was evaluated. During the treatment period, patients received 2 intravenous injections of S-151128 or placebo at 4-week intervals, and the safety, effectiveness of the drug, and pharmacokinetics were evaluated. The duration of participation in this study was up to approximately 16 weeks.

This study was run in Japan from December 2023 to July 2024.

Figure 1 Outline of the Study Schedule



4. WHAT PATIENTS WERE INCLUDED IN THIS STUDY?

For this study, patients who met the classification criteria for idiopathic knee osteoarthritis from the American College of Rheumatology, which is also used in Japan, and were diagnosed with knee osteoarthritis at least 3 months prior were asked to participate.

This was a "double-blind (observer-blind)" study. "Double-blind" means that neither the patients nor the study doctors knew who received S-151128 and who received a placebo during this study. A "placebo" is a dummy treatment that looks like S-151128 but does not contain active ingredients of S-151128 in it. A double-blind method helps make study results unbiased and fair. Since S-151128 can be distinguished from placebo by appearance, an observer-blind method was used where neither the patients nor the study doctors knew which study drug was injected, except for the staff who prepared the infusion. Patients in this study were randomly assigned to one of these groups to reduce the bias between the groups.

A total of 76 patients with knee osteoarthritis took part in this study: 38 patients in the S-151128 group (15 males, 23 females; mean age: 63.4 years) and 38 patients in the placebo group (11 males, 27 females; mean age: 61.3 years). Four patients (3 patients in the S-151128 group and 1 patient in the placebo group) left this study before it was done. The reason for leaving the study was consent withdrawal for these patients.

5. WHICH STUDY DRUGS WERE STUDIED?

The study drugs used in this study were S-151128 and placebo. Patients in each group received 2 intravenous injections of S-151128 360 mg or placebo at 4-week intervals. Patients were also given acetaminophen as a rescue medication if pain became intolerable during the study.

6. WHAT WERE THE OVERALL RESULTS OF THIS STUDY?

In this section, only key results are mentioned.

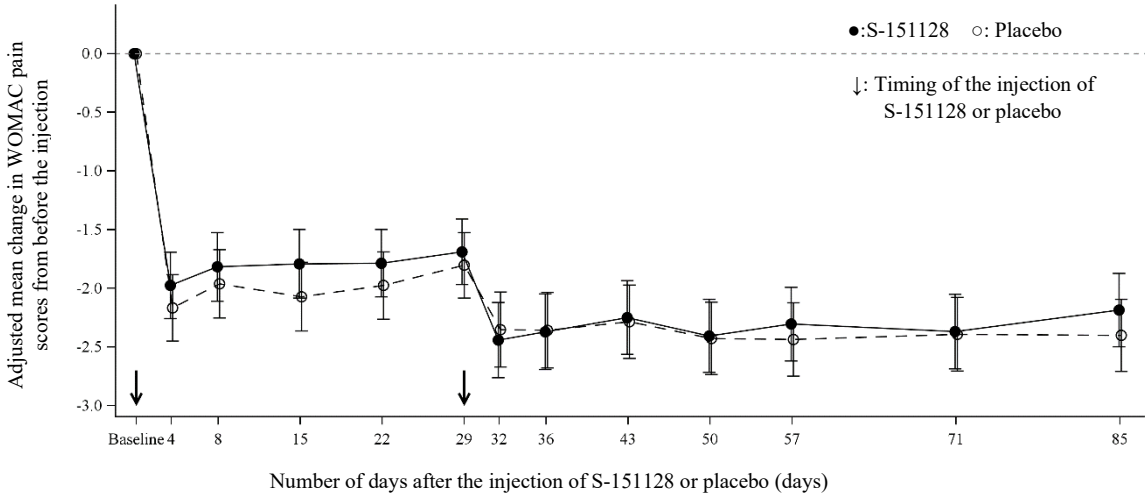
None of the patients in this study experienced serious side effects, and there were no clinically significant abnormal findings in the results of laboratory tests, 12-lead electrocardiography, or imaging assessment of the knee joint. The details of side effects observed in this study are shown in "7. WHAT WERE THE SIDE EFFECTS?."

Of the WOMAC scores before the injection of the study drug, the mean scores for pain (5 questions; hereinafter, the pain score) in the past 48 hours (higher scores indicate stronger pain) for each group were 6.28 points in the S-151128 group and 6.28 points in the placebo group, showing no differences between the groups.

The change in WOMAC pain score, indicated by the reduction in score compared to before the injection of the study drug, is shown in Figure 2. The mean WOMAC pain score on day 4 after the injection of the study drug compared to before the injection of the study drug was reduced by 1.98 points in the S-151128 group and 2.17 points in the placebo group (same order, hereinafter), 1.69 points and 1.80 points, respectively, on day 29, 2.44 points and 2.35 points, respectively, on day 32, 2.30 points and

2.44 points, respectively, on day 57, and 2.19 points and 2.40 points, respectively, on day 85. The results showed that the change in WOMAC pain score from before the injection of the study drug throughout the treatment period in the S-151128 group was comparable to or less than that in the placebo group.

Figure 2 Changes in WOMAC Pain Scores From Before the Injection of the Study Drug



Baseline: Before the injection of S-151128 or placebo

The change in WOMAC pain score from before the injection of S-151128 or placebo indicated an improvement in the pain when it was a negative value.

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 medical problems that patients have while they are in this study.

- An “adverse event” is a medical problem that happens in a patient during the study, whether or not it might be caused by a study drug taken.
- A “side effect” (unwanted effects) is an adverse event judged by the study doctor to be caused by a study drug used in the study.
- A “serious side effect” means a side effect 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 important state.

The side effects experienced by patients while taking part in this study are shown in Table 1. There were no serious side effects experienced by patients while taking part in this study.

Table 1 List of Side Effects

Side Effects	Number of Patients	
	S-151128 (out of 38 patients)	Placebo (out of 38 patients)
Injection site reaction	2 (5.3%)	0
Headache	1 (2.6%)	0
Abdominal discomfort	1 (2.6%)	0
Neck pain	1 (2.6%)	0
Feeling hot	1 (2.6%)	0
Urinary casts	1 (2.6%)	0
White blood cells urine positive	1 (2.6%)	0

Injection site reaction: Symptoms such as redness, hardening, itchiness, pain, blisters, or infection at the injection site

Urinary casts: Cylindrical shaped aggregation of urinary components found in urine in urinalyses

White blood cells urine positive: White blood cells found in urine in urinalyses

8. HOW HAS THIS STUDY HELPED PATIENTS AND RESEARCHERS?

The results are limited to the particular patients from this study 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 obtained in other studies. However, this research helps future patients and families by helping researchers understand more about each drug being studied.

9. ARE THERE PLANS FOR FURTHER STUDIES?

There are no currently ongoing studies with S-151128, and no future studies are planned in patients with knee osteoarthritis at this time.

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

You may find more information about this study on the following websites:

Website	URL	Identifier
SHIONOGI	English: https://www.shionogi.com/global/en/innovation/randd/clinical-development/clinical-trial-data/clinical-trial01.html	Protocol No.: 2303VA612
jRCT	Japanese: https://jrct.mhlw.go.jp/latest-detail/jRCT2031230458	number of clinical trial plan: jRCT2031230458

Contact information for the company that conducted this study:

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