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ORIGINAL RESEARCH

# Efficacy and safety of controlled-release oxycodone for the management of moderate-to-severe chronic low back pain in Japan: results of an enriched enrollment randomized withdrawal study followed by an open-label extension study

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Mikito Kawamata[1]
Masako Iseki[2]
Mamoru Kawakami[3]
Shoji Yabuki[4]
Takuma Sasaki[5]
Mitsuhiro Ishida[5]
Atsushi Nishiyori[5]
Hideaki Hida[6]
Shin-ichi Kikuchi[4]

[1]Department of Anesthesiology and Resuscitology, Shinshu University School of Medicine, Matsumoto, Japan; [2]Department of Anesthesiology and Pain Medicine, Juntendo University Faculty of Medicine, Tokyo, Japan; [3]Spine Care Center, Wakayama Medical University Kihoku Hospital, Wakayama, Japan; [4]Department of Orthopaedic Surgery, Fukushima Medical University School of Medicine, Fukushima, Japan; [5]Clinical Development Department, Shionogi & Co. Ltd., Osaka, Japan; [6]Biostatistics Center, Shionogi & Co. Ltd., Osaka, Japan

**Background:** Oxycodone is one of the options for the management of CLBP in patients with an inadequate response to other analgesics. However, oxycodone is not yet approved for noncancer pain in Japan. Here, we assessed the efficacy and long-term safety of S-8117, a controlled-release oxycodone formulation, for the management of Japanese CLBP patients.

**Patients and methods:** An initial enriched enrollment randomized withdrawal, double-blind, placebo-controlled, 5-week phase III trial was conducted across 54 centers in Japan to assess the efficacy of S-8117 vs placebo in moderate-to-severe CLBP patients. Subsequently, a 52-week, open-label, single-arm study was conducted across 53 centers in Japan to evaluate the long-term safety of S-8117. The primary endpoint was the time to inadequate analgesic response during 35 days of the double-blind period. Secondary endpoints were the percentages of patients with inadequate analgesic response, discontinuation rate due to inadequate analgesic effects or AEs, and changes in scores of BPI severity, BPI pain interference, SF-36, and Roland-Morris Disability Questionnaire. Safety was assessed as the incidence of AEs and ADRs.

**Results:** Of the 189 patients enrolled in the double-blind study, 130 patients who completed the initial titration period were randomized 1:1 to receive either S-8117 (n=62) or placebo (n=68). Baseline characteristics were comparable across the study groups. The time to inadequate analgesic response was significantly longer in patients treated with S-8117 than placebo ($P$=0.0095). Secondary endpoints corroborated the efficacy of S-8117 vs placebo. Overall, 478 AEs were reported in 73/75 patients in the long-term study. The most frequent ADRs were somnolence, constipation, and nausea. No case of drug dependence was reported in the long-term study.

**Conclusion:** Short-term efficacy vs placebo and long-term safety of S-8117 were demonstrated for the management of Japanese patients with moderate-to-severe CLBP.

**Keywords:** chronic low back pain, opioids, oxycodone, RCT

## Plain language summary

### Why was the study done?

We performed two phase III trials to study whether controlled-release oxycodone would safely provide pain relief for CLBP patients in Japan, where options for pharmacological management of noncancer chronic pain are limited; even some of the globally prescribed opioids, such as oxycodone, are yet to be approved. Although short-acting morphine and transdermal fentanyl patches have been approved as strong opioids for the management of CLBP in Japan, controlled-release oral formulations are not available yet.

Correspondence: Mikito Kawamata
Department of Anesthesiology and Resuscitology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
Tel +81 263 37 2667
Fax +81 263 35 2734
Email kawamata@shinshu-u.ac.jp

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## What did the researchers do and find?

We conducted a 5-week, randomized, double-blind trial to determine whether controlled-release oxycodone provided pain relief for a longer time in CLBP patients vs placebo. In the subsequent long-term study, we investigated the safety of controlled-release oxycodone in Japanese patients for a year. Results from our studies were positive in the given time periods and patient populations.

## What do the results mean?

Our results showed that Japanese CLBP patients who took controlled-release oxycodone had pain relief for a longer time compared with those who did not. Patients in both studies had typical side effects that are usually expected with opioid use. There was no cause for any additional concern regarding drug abuse or dependence in these studies. Controlled-release oxycodone could be a management option for patients with CLBP in Japan.



# Introduction

CLBP, which affects nearly 23% of the global population,[1] is also the most frequently reported type of chronic pain in Japan.[2–4] In the USA[5] and Europe,[1] opioids are used for the pharmacological management of noncancer chronic pain, including CLBP, in patients who experience an inadequate analgesic response to nonopioid drugs. Pain relief and functional improvement effects of opioids, albeit short-term, have been demonstrated in patients with chronic pain conditions such as CLBP.[6] Besides, serious safety concerns have been raised against the chronic use of opioids due to the risk of drug overdose, dependence, and abuse.[7] Given the equivocal risk–benefit profile,[8] careful use of opioids for the management of CLBP is a major clinical concern in Japan. Although opioids are widely used for cancer pain management in Japan, the number of available opioid drugs and the rate of consumption in patients with noncancer pain are limited compared with Western countries.

S-8117 (OxyContin®, Purdue Pharma LP, Stamford, CT, USA), an oral, controlled-release formulation of oxycodone hydrochloride (licensed by Mundipharma KK), is indicated for around-the-clock analgesia in patients with moderate-to-severe pain.[9] The efficacy of an extended-release formulation of oxycodone for the management of patients with CLBP was demonstrated in a randomized, double-blind, placebo-controlled study in the USA.[10] In Japan, S-8117 was approved in 2003 for the management of cancer pain; however, to date, no studies have specifically evaluated the efficacy of S-8117 in Japanese patients with noncancer chronic pain. Accordingly, S-8117 is not indicated for noncancer chronic pain in Japan. Therefore, we performed a randomized, double-blind study and an open-label, long-term study to assess both the short-term efficacy vs placebo and the long-term safety of S-8117, respectively, in Japanese CLBP patients.

# Patients and methods

## Study design

The investigation comprised two phase III studies: an initial EERW, double-blind, placebo-controlled study, followed by a subsequent 52-week, open-label, long-term study. Both studies were conducted in Japan: the first at 54 centers from October 2013 to June 2015 and the second at 53 centers from December 2013 to June 2016 (Figure 1).

The double-blind study was subdivided into four periods: an open-label dose-titration period (14–28 days), a double-blind period (35 days), a tapering period (7 days), and a follow-up period (7 days). The long-term study was subdivided into three periods: a long-term administration period (52 weeks), a tapering period (7 days), and a follow-up period (7 days).

## Patients

For the double-blind study, we enrolled men and women aged between 20 and 79 years, diagnosed with noncancer-related CLBP lasting ≥12 weeks, and a BPI[11] 24-hour average pain intensity score ≥4 prior to the registration despite management for ≥14 days with oral, patch, or suppository nonopioid analgesics including analgesic adjuvants or opioid analgesics (doses were prespecified as follows: oral codeine, ≤800 mg/day; oral morphine, ≤120 mg/day; and fentanyl patch, ≤100 μg/hour). Patients completing the double-blind study were eligible for inclusion in the long-term study. Major exclusion criteria of the double-blind study included comorbid pain conditions with potential influence on the study assessments, diagnosed psychogenic CLBP (determined by the investigator using the BS-POP questionnaire),[12] ongoing treatment for diagnosed psychiatric disorders, or hypersensitivity to or contraindication for opioids. Patients with a history of malignant tumor within 5 years, drug abuse, drug or alcohol dependence (determined by a urine drug test and interview by the investigator), or significant ADRs to in-progress or potential concomitant administration of opioids and central nervous system depressants during the study were also excluded. At the time of enrollment, patients underwent a urine test for the presence of phencyclidine, cocaine-type narcotics, stimulants, and cannabis, and those who tested positive were excluded from the study. In addition, patients who tested negative were excluded if they were diagnosed with or suspected of drug abuse or drug/alcohol dependence by

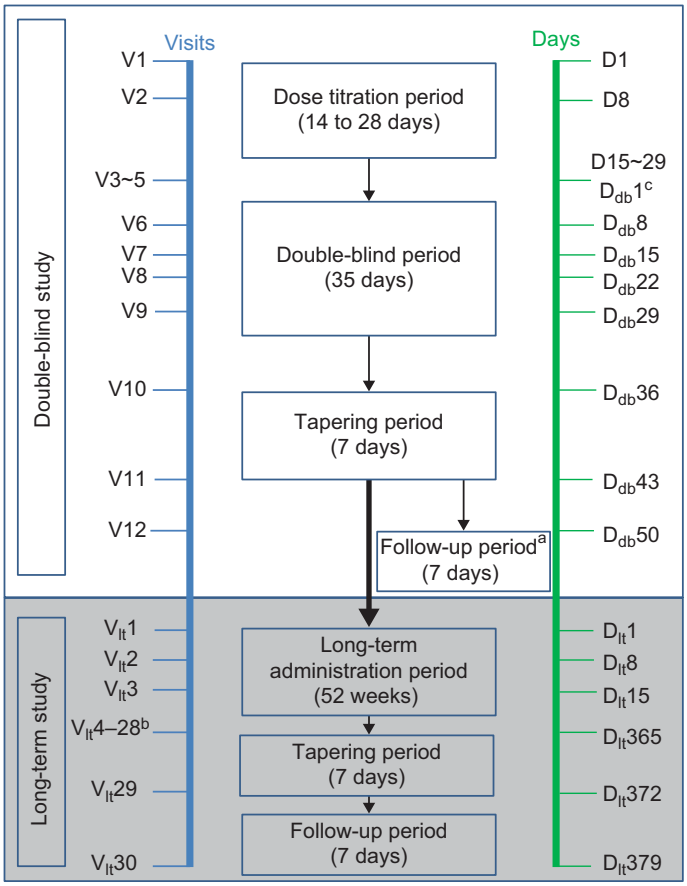


**Figure 1** Study design.
**Notes:** [a]Follow-up period for patients who did not transition to the long-term phase. [b]Patients were to appear once every 2 weeks between $V_{lt}3$ and $V_{lt}28$ ($D_{lt}15$ and $D_{lt}365$).
**Abbreviations:** D, day; $D_{db}$, day in the double-blind study; $D_{db}1^{C}$, day 1 of the double-blind period which coincided with the end of the dose-titration period; $D_{lt}$, day in the long-term study; V, visit; $V_{lt}$, visit in the long-term study.

the investigator. Patients with a BS-POP score of ≥11 were diagnosed as having psychogenic CLBP by the investigator and were excluded from the study.

Both studies are registered with the JapicCTI registry: double-blind study, JapicCTI-132299 and long-term study, JapicCTI-132300.

## Treatment

Eligible patients initially entered the dose-titration period of the double-blind study; after a changeover with a prespecified time period for each type of previously prescribed opioid, the dose was titrated until patients met the transition criteria for the double-blind period. The starting dose was selected according to the dose of the previously prescribed analgesic (Table S1), and the dose was orally administered twice daily. Patients who were not on any opioids were initiated on a dose of 5 mg. Dose escalation was permitted when the BPI average pain intensity score was >3 or the improvement in the score was <30% compared with that at the time of enrollment (visit 1). However, dose escalation within 3 days of the previous dose escalation was not permitted. Dose escalation was permitted by 5 mg per single dose with a maximum permissible dose of 80 mg/day; for ≥10 and ≥20 mg/dose, 10 and 20 mg dose escalation, respectively, were also acceptable. The criteria for transitioning to the double-blind period were as follows: scheduled dose remained constant for 7 days, BPI 24-hour average pain intensity score improved to ≤3 or by >30% from the registration, no additions or dose increments of nonopioid analgesics or analgesic adjuvants, and no or tolerable AEs reported for 3 days prior to the evaluation (same time period applied except for the first criterion). Patients who met the transition criteria were randomized 1:1 in a double-blind manner using a randomization table to receive either S-8117 or placebo for 35 days at a constant dose from the end of the titration period. A statistical minimization method was used for randomization, with the

following two allocation factors: the dose of S-8117 and the change in BPI 24-hour average pain intensity score from visit 1, both at the end of the titration period. Patients who completed or discontinued the double-blind period entered a 7-day dose-tapering period, followed by a 7-day follow-up period. Discontinuation was considered when a patient had an inadequate analgesic response or when the investigator recognized the need to do so.

In the long-term study, patients received a starting dose of 5 mg S-8117 every 12 hours. The daily dose in the long-term administration period was adjusted based on the severity of the pain and AEs, with no upper limit for the daily dose. However, dose escalation within 3 days of the previous dose escalation was not permitted except up to the dose used at the end of the double-blind period. Patients who were not to be managed with other opioids after the long-term administration period or discontinuation of S-8117 entered a 7-day dose-tapering period, followed by a 7-day follow-up period. Patients who required management with other opioid analgesics switched the medication after the long-term administration period or discontinuation of S-8117.

## Efficacy

The primary endpoint of the double-blind study was the time to inadequate analgesic response assessed from randomization (baseline) through day 36. Patients were defined as having an inadequate analgesic response if they met any of the following criteria: 1) aggravation leading to dose escalation or change or addition of analgesic (dose reduction and discontinuation were acceptable), including rescue treatment but excluding ≤3 consecutive days of treatment for AEs such as fever or 2) BPI 24-hour average pain intensity score remained >3 or improved by <30% from the registration for 3 consecutive days. The assessment was performed every day since the first day of administration of S-8117 or placebo through day 36 (or discontinuation). BPI pain intensity (worst, least, average, and current pain) was recorded by patients in a paper-based diary on a daily basis and confirmed by the investigator at each study visit.

Secondary efficacy endpoints in the double-blind study included the percentages of patients with inadequate analgesic response and who discontinued due to an inadequate analgesic effect or AEs and changes in BPI pain severity score, BPI pain interference score, SF-36 score, and level of physical disability according to the RDQ. Data collection for BPI pain severity score was scheduled on each day of the double-blind period and at the end of the tapering period. BPI pain interference scores were collected on each visit from visits 1 to 10 (or discontinuation) and at the end of the tapering period (or discontinuation) and confirmed by the investigator. The SF-36 and RDQ assessments were recorded on visits 1 and 5 (or when the patient achieved the transition criteria for the double-blind period) and 10 (or discontinuation) and confirmed by the investigator.

No primary efficacy endpoint was scheduled for the long-term study. Secondary efficacy endpoints included changes in BPI pain severity score from the end of the titration period of the double-blind study and in BPI pain interference score, SF-36 score, and level of physical disability by RDQ score from visit 1 of the double-blind study. In the long-term study, BPI pain severity and BPI pain interference were recorded at each visit; the SF-36 score was recorded at visits 14 and 28 (or discontinuation) and the RDQ score was recorded at visits 8, 14, 20, 26, and 28 (or discontinuation) by the patient on a questionnaire and confirmed by the investigator.

## Safety

Safety was assessed in all patients who received ≥1 dose of S-8117. Safety endpoints of both studies included the incidence of AEs and ADRs, the primary endpoint in the long-term study, and changes in vital signs, 12-lead electrocardiogram, and clinical laboratory tests. AEs were coded using the Medical Dictionary for Regulatory Activities version 18.0, and severity was classified using the Common Terminology Criteria for Adverse Events version 4.0. Drug withdrawal syndrome was assessed using a self-reported questionnaire based on the SOWS and an objective evaluation by the investigators using questions from the COWS. Drug dependency was evaluated using the D-2-A and D-2-B questionnaires[13] (Table S2). If the investigators detected withdrawal signs and symptoms or suspected drug dependency, such observations were prespecified to be reported to the Data and Safety Monitoring Board, which would make the final assessment.

## Statistical analyses

We estimated that a sample size of 63 patients per treatment group would provide an overall power of at least 90% at a two-sided significance level of 0.05 using Fisher's exact test to detect a difference in the rate of inadequate analgesic response in the double-blind study. Allowing for a 30% margin of patients who would not qualify for inclusion in the double-blind period of the study after the titration period, we determined that a total of 180 patients were required to undergo drug titration in the double-blind study. Assuming a discontinuation rate of about 20% due to inadequate analgesic response, ~100 patients were estimated to complete the double-blind study. Of these 100 patients, 80% were expected to transition to the long-term study. Therefore, a sample size of 80 was set for the long-term study.

The FAS included patients who received ≥1 dose of S-8117 and had BPI pain severity scores assessed at baseline and at least once after initiating treatment. The FAS2 included patients who transitioned into the double-blind study and received ≥1 dose of either S-8117 or placebo and had their BPI assessed at least once in the double-blind period. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). Missing data were imputed using the last observation carried forward method. The time to inadequate analgesic response in the double-blind study was compared between the treatment groups by the stratified log-rank test, adjusted by the allocation factors. The proportion of inadequate analgesic response and the proportion of discontinuation due to inadequate analgesic response or AEs in the double-blind study were compared between the treatment groups using the Mantel–Haenszel test with stratified factors. The changes from baseline to the end of the double-blind study in BPI pain severity (each of worst, least, average, and current pain), BPI pain interference, and SF-36 and RDQ scores were compared between the treatment groups using an analysis of covariance model, with treatment group as the fixed effect and baseline value and stratified factors as covariates in FAS2. Comparisons among treatment groups were based on the least squares mean for each treatment group. The incidence rates of AEs were compared between the treatment groups using Fisher's exact test. All statistical tests were performed at a two-sided significance level of 0.05.

## Ethics approval and informed consent

The clinical studies (JapicCTI-132299 and JapicCTI-132300) were conducted in accordance with the Declaration of Helsinki (1996) and Good Clinical Practice guidelines. Additionally, the local ethics committees (institutional review boards) (Table S3) approved the study protocol. Written informed consent was obtained from all participants before study commencement.

## Results

Of the total 189 patients registered, 188 underwent drug titration and were included in the FAS. Of these 188 patients, 130 patients (FAS2) were randomized 1:1 to receive either S-8117 (n=62) or placebo (n=68). Out of 83 patients who completed the double-blind study (46/62 in the S-8117 group and 37/68 in the placebo group), 75 patients transitioned into the open-label long-term study (Figure 2). No differences were noted in the baseline characteristics of patients across the treatment groups in the double-blind study and the patients in the long-term study (Table 1).

### Efficacy and safety of S-8117 in the double-blind study

#### Efficacy

Kaplan–Meier estimates showed that the patients in the S-8117 group had a significantly longer time to inadequate analgesic response than the patients in the placebo group ($P$=0.0095) (Figure 3). On day 36 of treatment in the double-blind study, the proportion of patients who had sufficient pain relief (95% CI) was 78.3% (65.5–86.8) in the S-8117 group and 58.2% (45.4–68.9) in the placebo group. The efficacy of S-8117 was further substantiated by data from the secondary endpoints (Table 2). Significant improvements were observed in the rate of inadequate analgesic effect, discontinuation rate due to inadequate analgesic effect or AEs, change in BPI pain severity score (least pain), change in BPI pain interference score (general activity), and change in SF-36 score (role physical).

#### Safety

During the titration period, 152 (80.9%) of 188 patients (FAS) developed AEs and 145 (77.1%) patients developed ADRs. During the double-blind period, 90 AEs were reported in 45 of 62 (72.6%) patients in the S-8117 group and 77 AEs in 37 of 68 (54.4%) patients in the placebo group (Table 3); 50 ADRs were reported in 31 of 62 (50.0%) patients in the S-8117 group and 38 ADRs in 21 of 68 (30.9%) patients in the placebo group. The most frequently reported ADRs in the S-8117 group during the double-blind period were somnolence (12.9%), malaise (6.5%), and constipation, vomiting, and decreased appetite (4.8%).

The incidence of AEs and ADRs was significantly higher in the S-8117 group vs placebo group during the double-blind period; however, this did not lead to increased discontinuation rates in the S-8117 group. Three SAEs were reported in two of 62 (3.2%) patients in the S-8117 group, but none were treatment-related. No SAEs were reported in the placebo group. During the dose-titration period, two SAEs were reported in two patients; one was determined to be unrelated and the other, deterioration of pre-existing cataract, was possibly related to S-8117.

No notable differences in total COWS and SOWS scores were observed between the groups. The change from baseline to final evaluation in the total COWS scores (mean ± SD) was −0.1±1.0 and −0.4±1.4 in the S-8117 and placebo groups, respectively, and the change from baseline to final evaluation in the total SOWS scores (mean ± SD) was −0.5±3.6 and −1.2±3.2 in the S-8117 and placebo groups, respectively. No clinically meaningful withdrawal symptoms were observed in any patient as per the results of the assessments using the COWS and SOWS scores. The change from baseline to final evaluation in the total COWS and SOWS scores (mean ± SD)

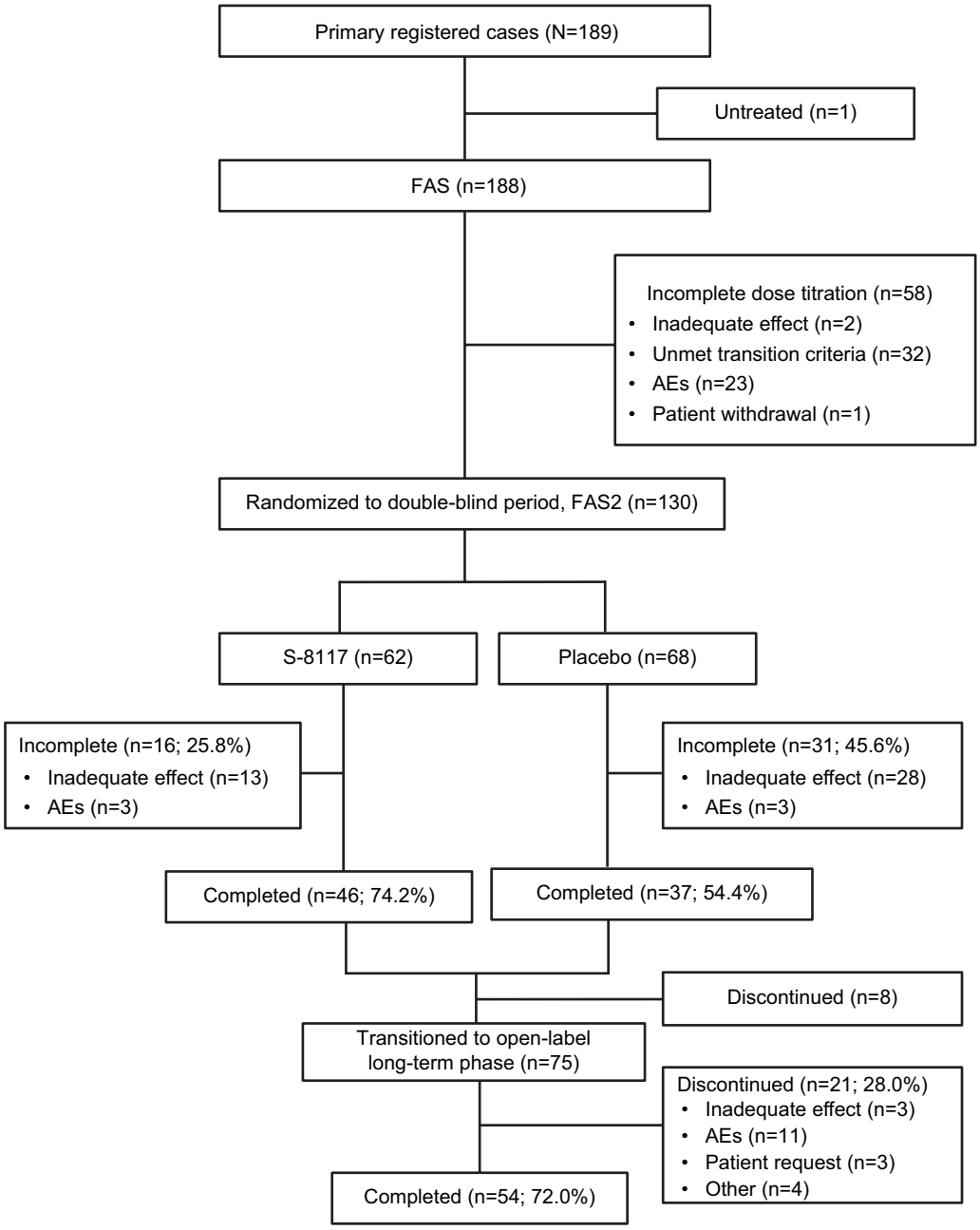


**Figure 2** Patient disposition.
**Notes:** FAS comprised patients who received ≥1 dose of S-8117 and had the BPI pain severity score assessed at baseline and on ≥1 visit after the start of treatment; FAS2 comprised patients who transitioned into the double-blind period, received ≥1 dose of S-8117 or placebo, and had the BPI pain severity data assessed at ≥1 visit after the start of the double-blind period.

was −0.3±1.0 and −1.1±3.3, respectively. No patients were judged to have developed drug dependency by the Data and Safety Monitoring Board.

## Safety and efficacy of S-8117 in the long-term study

Patients in the long-term study received an average daily dose of 24.86 mg in S-8117, whereas the average daily dose at the end of the titration period of the double-blind study was 31.90 mg. During the long-term study, there were no reports of any newly emerged serious ADRs or clinically relevant concerns. A total of 403 treatment-emergent AEs were reported in 71 patients during the long-term administration period; additionally, 75 AEs in 37 patients were carried over from the double-blind study. Overall, 478 AEs were reported in 73 of 75 (97.3%) patients throughout the long-

**Table 1** Baseline demographics and characteristics

| Characteristics | Double-blind study (FAS2; N=130) | | Long-term study |
|---|---|---|---|
| | S-8117 | Placebo | (n=75) |
| | (n=62) | (n=68) | |
| Age, years, mean (SD) | 62.8 (13.2) | 64.9 (12.0) | 63.8 (13.2) |
| Sex, n (%) | | | |
| Male | 33 (53.2) | 32 (47.1) | 42 (56.0) |
| Female | 29 (46.8) | 36 (52.9) | 33 (44.0) |
| Race, n (%) | | | |
| Asian | 62 (100.0) | 68 (100.0) | 75 (100.0) |
| Inpatient/outpatient, n (%) | | | |
| Inpatient | 1 (1.6) | 0 | – |
| Outpatient | 61 (98.4) | 68 (100.0) | – |
| Height, cm, mean (SD) | 158.8 (8.7) | 159.0 (9.6) | – |
| Weight, kg, mean (SD) | 58.8 (11.8) | 59.2 (12.7) | – |
| Diagnosis, n (%) | | | |
| Lumbar spinal stenosis | 16 (25.8) | 27 (39.7) | 24 (32.0) |
| Spinal osteoarthritis | 4 (6.5) | 5 (7.4) | 3 (4.0) |
| Degenerative spondylolisthesis | 3 (4.8) | 1 (1.5) | 2 (2.7) |
| Degenerative lumbar scoliosis | 4 (6.5) | 2 (2.9) | 4 (5.3) |
| Intervertebral disc herniation | 7 (11.3) | 9 (13.2) | 8 (10.7) |
| Failed back surgery syndrome | 13 (21.0) | 11 (16.2) | 12 (16.0) |
| Other | 15 (24.2) | 13 (19.1) | 22 (29.3) |

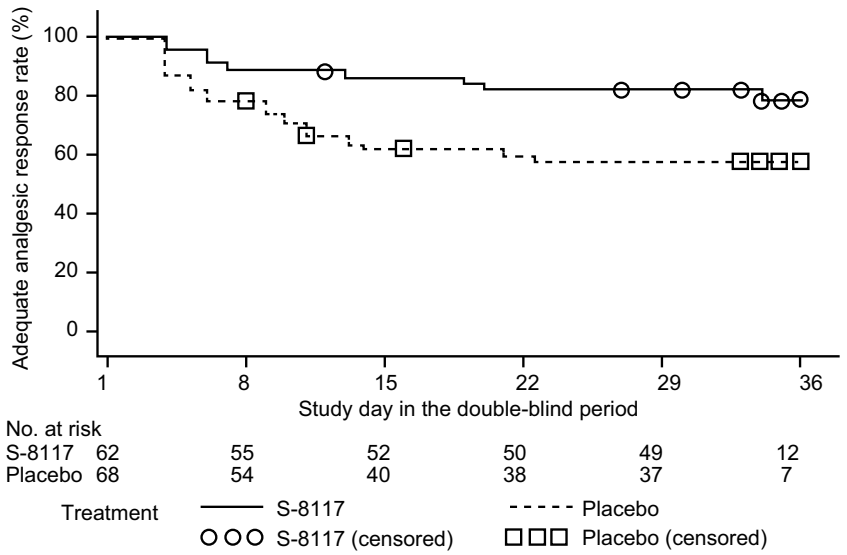


**Figure 3** Kaplan–Meier curve for the time to inadequate analgesic response (FAS2).
**Notes:** FAS2 comprised patients who transitioned into the double-blind period, received ≥1 dose of S-8117 or placebo, and had the BPI pain severity data assessed at ≥1 visit after the start of the double-blind period.

term study (Table 4). The most common ADRs (≥5% incidence) that newly emerged during the long-term study were somnolence (24.0%), constipation (17.3%), nausea (17.3%), dizziness (6.7%), vertigo (6.7%), and vomiting (5.3%). In 12 of 75 patients, AEs or ADRs led to withdrawal of the study drug. No case of withdrawal symptom was reported in the current study as per the results of the assessments with the SOWS and COWS scores. No patient was ascertained to be a case of psychological dependence by the Data and Safety Monitoring Board.

For all evaluation time points, including the final evaluation during the long-term administration period, average BPI pain scores for the average, worst, and current pain decreased compared with the end of the titration period of

**Table 2** Double-blind study secondary endpoints

| Summary of secondary endpoints (FAS2) | Statistic | S-8117 (N=62) | Placebo (N=68) | *P*-value |
|---|---|---|---|---|
| Rate of inadequate analgesic effect | n (%) | 13 (21.0) | 28 (41.2) | 0.0136 |
| Discontinuation rate due to inadequate analgesic effect or AEs | n (%) | 16 (25.8) | 31 (45.6) | 0.0190 |
| Change in BPI pain severity score | | | | |
| Average pain | LS mean (SE) | 0.1 (0.2) | 0.5 (0.2) | 0.0600 |
| Worst pain | LS mean (SE) | 0.0 (0.2) | 0.4 (0.2) | 0.2639 |
| Least pain | LS mean (SE) | 0.1 (0.1) | 0.6 (0.1) | 0.0051 |
| Current pain | LS mean (SE) | 0.1 (0.2) | 0.6 (0.2) | 0.0672 |
| Change in BPI pain interference score | | | | |
| General activity | LS mean (SE) | −0.3 (0.2) | 0.7 (0.2) | 0.0028 |
| Mood | LS mean (SE) | 0.0 (0.3) | 0.4 (0.3) | 0.3156 |
| Walking ability | LS mean (SE) | 0.0 (0.3) | 0.5 (0.2) | 0.1550 |
| Normal work | LS mean (SE) | −0.1 (0.2) | 0.4 (0.2) | 0.0914 |
| Relations with other people | LS mean (SE) | 0.1 (0.2) | 0.2 (0.2) | 0.6213 |
| Sleep | LS mean (SE) | −0.1 (0.2) | 0.3 (0.2) | 0.2372 |
| Enjoyment of life | LS mean (SE) | 0.0 (0.3) | 0.5 (0.2) | 0.1866 |
| Average of the seven items | LS mean (SE) | −0.05 (0.21) | 0.43 (0.20) | 0.1018 |
| Change in SF-36 | | | | |
| Physical functioning | LS mean (SE) | 0.19 (2.05) | −1.28 (1.94) | 0.6052 |
| Role physical | LS mean (SE) | 6.91 (2.51) | −0.63 (2.37) | 0.0305 |
| Bodily pain | LS mean (SE) | 3.34 (1.74) | 0.43 (1.64) | 0.2263 |
| General health | LS mean (SE) | −0.01 (1.54) | −2.78 (1.45) | 0.1921 |
| Vitality | LS mean (SE) | 2.43 (2.13) | 0.17 (2.01) | 0.4447 |
| Social functioning | LS mean (SE) | −1.54 (2.29) | 2.77 (2.16) | 0.1785 |
| Role emotional | LS mean (SE) | 1.79 (2.49) | 0.44 (2.36) | 0.6926 |
| Mental health | LS mean (SE) | 2.85 (1.79) | 2.08 (1.69) | 0.7537 |
| Change in RDQ | LS mean (SE) | 0.1 (0.5) | 1.2 (0.4) | 0.0677 |

**Abbreviations:** LS, least squares; SE, standard error.

**Table 3** AEs during the dose-titration and double-blind periods of the double-blind study

| n (%) | Open-label titration period | Double-blind period | | *P*-value |
|---|---|---|---|---|
| | (N=188) | S-8117 (n=62) | Placebo (n=68) | |
| Number of AEs | 425 | 90 | 77 | |
| Patients with AEs | 152 (80.9) | 45 (72.6) | 37 (54.4) | 0.0450 |
| Patients with ADRs | 145 (77.1) | 31 (50.0) | 21 (30.9) | 0.0320 |
| Patients with SAEs | 2 (1.1) | 2 (3.2) | 0 | 0.2255 |
| Patients with serious ADRs | 1 (0.5) | 0 | 0 | |
| Patients with significant AEs | 26 (13.8) | 2 (3.2) | 2 (2.9) | 1.0000 |
| Patients with significant ADRs | 25 (13.3) | 2 (3.2) | 2 (2.9) | 1.0000 |
| Patients with AEs leading to treatment discontinuation | 26 (13.8) | 2 (3.2) | 2 (2.9) | 1.0000 |
| Patients with ADRs leading to treatment discontinuation | 24 (12.8) | 1 (1.6) | 2 (2.9) | 1.0000 |
| Patients with AEs leading to death | 0 | 0 | 0 | |

**Note:** Patients who received at least one dose of S-8117 comprised the safety set and were evaluated for safety.

the double-blind study. Although the least pain score showed a reduction on day 15 (visit 3) and later evaluation points, a slight increase was noted at the final evaluation. The scores of BPI pain interference, SF-36, and RDQ indicated overall improvement (data not shown).

## Discussion

This EERW, placebo-controlled, double-blind study demonstrated the efficacy of S-8117 vs placebo for the management of Japanese patients with CLBP. The subsequent open-label study demonstrated that long-term (52 weeks) management

**Table 4** Treatment-emergent AEs during the long-term study

| | AE (n=75) | ADR (n=75) |
|---|---|---|
| AEs/ADRs | | |
| Number of subjects | 73 | 59 |
| Number of events | 478 | 155 |
| Percentage of subjects | 97.3 | 78.7 |
| Deaths | | |
| Number of subjects | 0 | 0 |
| Serious AEs/ADRs | | |
| Number of subjects | 8 | 0 |
| Number of events | 10 | 0 |
| Percentage of subjects | 10.7 | 0 |
| Significant AEs/ADRs | | |
| Number of subjects | 10 | 5 |
| Number of events | 10 | 5 |
| Percentage of subjects | 13.3 | 6.7 |
| AEs/ADRs leading to treatment discontinuation | | |
| Number of subjects | 12 | 5 |
| Number of events | 13 | 5 |
| Percentage of subjects | 16.0 | 6.7 |

with S-8117 was tolerable and not associated with drug dependency. The primary endpoint of the double-blind study was met; time to inadequate analgesic response was significantly longer in the S-8117 group than in the placebo group during the double-blind period. Furthermore, the results of the secondary endpoints were in line with those of the primary endpoint. Although not directly comparable with this study, a previously published randomized, double-blind, short-term study (5 weeks) demonstrated the efficacy of a long-acting formulation of oxycodone vs placebo for the management of moderate-to-severe osteoarthritic pain.[14] Additionally, our results are consistent with a recent meta-analysis which concluded that short-term (≤3 months) management with opioids is more efficacious than placebo for pain relief and improvement in function in patients with CLBP.[6]

In the long-term study, no new ADRs were reported other than those already known in CLBP patients who are treated with opioids.[6] The most frequently reported ADRs during the long-term study were somnolence, constipation, and nausea, and these were mostly common during the double-blind study. Our results were consistent with a previous open-label long-term safety study of an extended-release formulation of oxycodone which showed that oxycodone was well tolerated in patients with CLBP over 12 months.[15]

All 75 patients in the long-term study were assessed for drug dependence. S-8117 did not induce any psychological dependence in our study, which may be attributable to the appropriate patient selection and periodic monitoring. However, given the limited number of patients and the inherent potential for drug dependency, we advise careful patient selection, periodic monitoring, and risk assessment for drug dependence in patients treated with opioids to limit the risk for abuse and overdose.[16,17]

Unlike Western countries, Japan has a low incidence of drug abuse, including that of opioids, and thus, no standard assessment procedures are established yet. In the current study, withdrawal syndrome was assessed by using questions from the SOWS and COWS. Although both questionnaires require practitioners to use the total scores to determine the severity of withdrawal symptoms, we used the change in score of each question, which enabled us to perform more detailed assessments. For the drug dependence assessment, investigators used the D-2-A and D-2-B questionnaires developed in Japan. Although not validated yet, we adopted these questionnaires because they have been used in a previous clinical trial of a drug with dependence-producing properties in Japan.[18] No clinically meaningful case of withdrawal syndrome or drug dependence was detected with the assessment procedures applied in the present study. However, standard assessment procedures will be required in Japan for continuous monitoring of such incidents in the clinical setting.

## Limitations of these studies

One of the known limitations of an EERW study design is that the results are only applicable to patients who show positive responses in the enrichment phase and proceed to the double-blind randomized study. In the current double-blind study, patients in the dose-titration period were required to fulfill the prespecified criteria regarding consistent response and tolerability to S-8117 in order to transition to the double-blind period. Besides, the long-term study population did not include patients who discontinued the double-blind study due to inadequate analgesic responses or AEs. Also, the population characteristics of the participants and Japanese CLBP patients with respect to their needs for opioid management may not be entirely comparable. For example, the study population could have skewed age distribution toward older ages. Therefore, the safety profile derived from the current study may not be applicable to the long-term clinical use of S-8117.

# Conclusion

The double-blind study demonstrated the short-term efficacy, and the long-term study suggested the safety of S-8117 for moderate-to-severe CLBP in Japanese patients with an inadequate analgesic response to nonopioid and opioid analgesic drugs. However, due to the limited information, the safety profile for chronic use of S-8117 in a clinical setting remains inconclusive. Based on the results of these studies, controlled-release oral

oxycodone presents a potential to be one of the options for the management of moderate-to-severe CLBP in Japan.

## Abbreviations

ADR, adverse drug reaction; AE, adverse event; BPI, Brief Pain Inventory; BS-POP, Brief Scale for Psychiatric Problems in Orthopedic Patients; CLBP, chronic low back pain; COWS, Clinical Opioid Withdrawal Scale; D-2-A, Dependency-2-A; D-2-B, Dependency-2-B; EERW, enriched enrollment randomized withdrawal; FAS, full analysis set; JapicCTI, Japan Pharmaceutical Information Center Clinical Trials Information; RDQ, Roland-Morris Disability Questionnaire; SAE, serious adverse event; SF-36, 36-Item Short Form Health Survey; SOWS, Subjective Opioid Withdrawal Scale.

## Data sharing statement

- Whether the authors intend to share individual deidentified participant data: No.
- What specific data they intend to share: Not available.
- What other study-related documents will be made available: Not available.
- How the data will be accessible: Not applicable.
- When and for how long they will be made available: Not applicable.

In order to provide public data access pertaining to the Shionogi-sponsored studies on the approved products, a data sharing system is currently under development along with a corresponding policy.

For further inquiry, please contact Takuma Sasaki at takuma.sasaki@shionogi.co.jp

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## Author contributions

All named authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

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# Supplementary materials

**Table S1** Selection criteria for dose of S-8117 in the dose-titration period according to dose of the previously prescribed analgesic before the changeover period

| Drug | Level | Previous drug daily administration dose | S-8117 daily administration dose (mg) |
|---|---|---|---|
| Oral morphine preparation (mg) | 1 | <30 | 10 |
| | 2 | ≥30 and <60 | 20 |
| | 3 | ≥60 and <90 | 40 |
| | 4 | ≥90 and <120 | 60 |
| | 5 | 120 | 80 |
| Oral codeine preparation (mg) | 1 | <200 | 10 |
| | 2 | ≥200 and <400 | 20 |
| | 3 | ≥400 and <600 | 40 |
| | 4 | ≥600 and <800 | 60 |
| | 5 | 800 | 80 |
| Fentanyl patch (μg/h) | 1 | 12.5 | 10 |
| | 2 | 25, 37.5 | 20 |
| | 3 | 50, 62.5 | 40 |
| | 4 | 75, 87.5 | 60 |
| | 5 | 100 | 80 |
| Buprenorphine patch (mg) | 1 | 5 | 10 |
| | 2 | 10, 20 | 20 |
| Tramadol formulation (mg) | 1 | <150 | 10 |
| | 2 | ≥150 | 20 |

**Table S2** Dependency-2-A (D-2-A) and Dependency-2-B (D-2-B) criteria used in the current study where applicable to the following questions, please mark ◯.

| Questions | | Remarkable | Moderate | Slight | None | Remarks (reason) |
|---|---|---|---|---|---|---|
| **D-2-A** | | | | | | |
| 1 | Do you feel clear headed on this drug? | | | | | |
| 2 | Do you feel indifferent to/disliked any person or thing on this drug? | | | | | |
| 3 | Do you become hyperactive or talkative on this drug? | | | | | |
| 4 | Do you become broad-minded on this drug? | | | | | |
| 5 | Do you feel intoxicated on this drug? | | | | | |
| 6 | Do you feel irritable or somewhat lonely when the drug effect runs out? | | | | | |
| 7 | Do you want to continue taking this drug? | | | | | |
| 8 | Do you think this drug became less effective? | | | | | |
| 9 | Do you want to take this drug in larger doses? | | | | | |
| 10 | Do you feel nauseated or tremulous when the drug effect runs out? | | | | | |
| **D-2-B** | | | | | | |
| 1 | Have you felt irritable or unstable after you were off this drug? | | | | | |
| 2 | Have you had more difficulty in sleeping after you were off this drug? | | | | | |
| 3 | Have you had nausea, vomiting, tremors of limb, or perspiration after you were off this drug? | | | | | |
| 4 | Do you really want to take this drug again? | | | | | |
| 5 | Have you had convulsions after you were off this drug? | | | | | |
| 6 | Have you had clouded mind or heard or seen anything unusual after you were off this drug? | | | | | |

**Note:** Patients meeting at least one of the following criteria were reported to the Data and Safety Monitoring Board as suspected cases of drug dependence: 1) Answered ≥1 of any question (except no. 7) as "remarkable" OR answered question 6 as "moderate" in the D-2-A questionnaire. 2) Answered ≥1 of any question (except no. 4) as "remarkable" OR answered question 1 or 3 as "moderate" in the D-2-B questionnaire. If question 7 in the D-2-A questionnaire or question 4 in the D-2-B questionnaire was answered as "remarkable," the decision to report the case to the Data and Safety Monitoring Board as a suspected case of drug dependence was based on the investigator's discretion because the answer could be associated with the analgesic effect.

**Table S3** List of approving local ethics committees (institutional review boards)

| |
|---|
| Asahikawa Medical University Hospital Institutional Review Board |
| Chiba University Hospital Institutional Review Board |
| Social Welfare Organization Saiseikai, Imperial Gift Foundation Inc. Chibaken Saiseikai Narashino Hospital Institutional Review Board |
| Chubu Rosai Hospital Institutional Review Board |
| Eniwa Hospital Institutional Review Board |
| Fukushima Medical University Hospital Institutional Review Board |
| Hakodate Central General Hospital Institutional Review Board |
| Hiroshima City Asa Citizens Hospital Institutional Review Board |
| Hiroshima Clinic Institutional Review Board |
| Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital Institutional Review Board |
| Juntendo University Hospital Institutional Review Board |
| Junwakai Memorial Hospital Institutional Review Board |
| Keio University Hospital Institutional Review Board |
| The Institutional Review Board of Kitasato University Shirokane Campus |
| Kobe University Hospital Institutional Review Board |
| Kondo Memorial Medical Foundation Tomisaka Clinic Institutional Review Board |
| Kurume University Hospital Institutional Review Board |
| Kyorin University Hospital Institutional Review Board |
| Marunouchi Hospital Institutional Review Board |
| Mie University Hospital Institutional Review Board |
| Nagasaki Rosai Hospital Institutional Review Board |
| National Hospital Organization Chiba Medical Center Institutional Review Board |
| Nihonbashi Sakura Clinic Institutional Review Board |
| Niigata University Medical & Dental Hospital Institutional Review Board |
| Nippon Life Hospital Institutional Review Board |
| NTT Medical Center Tokyo Institutional Review Board |
| Ogikubo Hospital Institutional Review Board |
| Oita Central Institutional Review Board |
| Oita University Hospital Institutional Review Board |
| Onishi Medical Clinic Institutional Review Board |
| Saga Medical Centre Koseikan Institutional Review Board |
| Saga University Hospital Institutional Review Board |
| Sendai Institutional Review Board |
| Shimane University Hospital Institutional Review Board |
| Shinagawa Clinic Institutional Review Board |
| Shin-Kokura Hospital Institutional Review Board |
| Shinshu University Hospital Institutional Review Board |
| Teikyo University Chiba Medical Center Institutional Review Board |
| The University of Tokyo Hospital Institutional Review Board |
| Tokushukai Group Institutional Review Board |
| Toyama University Hospital Drug Acceptance Research Review Board |
| Tsuchiura Kyodo General Hospital Institutional Review Board |
| Tsukuba Gakuen Hospital Institutional Review Board |
| University of Fukui Hospital Institutional Review Board |
| Yasuda Hospital Institutional Review Board |