2. SYNOPSIS

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Study Title:
A phase 2a study of S-637880 in patients with neuropathic low back pain

Investigators and Study Sites: This study was a multicenter study conducted at 31 sites in Japan.

Publication (reference): Not applicable

Studied Period: From 11 Mar 2021 to [redacted]

Phase of Development: Phase 2

Objectives and Endpoints:

Objectives	Endpoints
Primary	
● To assess the efficacy of S-637880 in patients with neuropathic low back pain.	● Change from baseline in the mean weekly numerical rating scale (NRS) score of worst daily leg pain after 8 weeks of treatment
Secondary	
● To assess the efficacy of S-637880 in patients with neuropathic low back pain.	● Change from baseline in the mean weekly NRS score of: – Average daily leg pain – Worst daily low back pain – Average daily low back pain ● Time to 30% or 50% improvement in the mean weekly NRS score of: – Worst daily leg pain – Average daily leg pain – Worst daily low back pain – Average daily low back pain ● Change from baseline in Neuropathic Pain Symptom Inventory (NPSI) score ● Patient global impression of improvement (PGI-I) score ● Change from baseline in clinical global

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	impression – severity (CGI-S) score • Change from baseline in Oswestry Disability Index (ODI) score • Change from baseline in Short-Form (36) Health Survey (SF-36) score • Change from baseline in European Quality of Life Questionnaire – 5 Dimensions – 5 Levels (EQ-5D-5L) score • Change from baseline in Patient Health Questionnaire – 9 (PHQ-9) score • Change from baseline in a Revised Version of the Medical Outcomes Study Sleep Scale (MOS-SS-R) score • Change from baseline in Perceived Deficits Questionnaire – 5 (PDQ-5) score • The percentage of participants who received rescue medicines
• To assess the safety and tolerability of S-637880 in patients with neuropathic low back pain.	• Discontinuation rate due to adverse events (AEs) • Serious adverse events (SAEs) • AEs of special interest (AESI) • AEs/treatment-related AEs (TEAEs) • Laboratory values • Body weight • Vital signs • 12-lead electrocardiography (ECG) • Columbia-suicide severity rating scale (C-SSRS)
• To assess the pharmacokinetics (PK) of S-637880 and its major metabolite S-637880 demethyl.	• Plasma S-637880 concentration, plasma S-637880 demethyl concentration
Exploratory	
• [redacted]	[redacted]

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• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Methodology:

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. This study consisted of 3 periods (10 to 13 weeks in total): Pretreatment Observation Period (1 to 4 weeks), Intervention Period (8 weeks), and Follow-up Period (1 week). Participants who were confirmed to be eligible during the Pretreatment Observation Period were randomly assigned at a ratio of 1:1 to either the S-637880 group or the placebo group. The randomization was performed using the stochastic minimization method. The stratification factors for randomization were painDETECT score at Visit 2 (< 13, ≥ 13), weekly mean of maximum daily pain intensity in the leg (< 7, ≥ 7) at baseline as measured on the NRS at Visit 2, and disease (specific chronic low back pain, non-specific chronic low back pain). During the Intervention Period, participants orally received the study intervention (20 mg of S-637880 or placebo) twice daily for 8 weeks in a double-blind manner. The Follow-up Visit (Visit 8) was performed no less than 7 days after the last dose of study intervention.

The administration of S-637880 could cause drug eruption. Therefore, a Safety Monitoring Committee, a third-party organization independent from the sponsor, was established to evaluate the risk of drug eruption from a fair and impartial perspective on the basis of the safety information collected during the study, especially AEs related to the skin.

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Number of Participants (Planned and Analyzed):

Planned: 160 randomized participants (80 participants per group)

Randomized: 51 participants (25 in the S-637880 group, 26 in the placebo group)

Analyzed for efficacy:

- Intention-to-treat (ITT):
  51 participants (25 in the S-637880 group, 26 in the placebo group)
- Per protocol set (PPS):
  44 participants (21 in the S-637880 group, 23 in the placebo group)

Analyzed for safety:

- Safety analysis population:
  51 participants (25 in the S-637880 group, 26 in the placebo group)

Analyzed for PK:

- PK Population:
  25 participants

Diagnosis and Main Criteria for Inclusion:

1. Inclusion criteria

- Male or female outpatients aged 20 to < 75 years at the time of signing the informed consent
- Participants who met all of the following criteria of neuropathic low back pain
  - Participants with chronic pain present on the posterior surface of the trunk between the twelfth rib and the inferior end of the gluteal fold
  - Participants with radiating pain along dermatome L4, L5 or S1 of lower extremities (hereinafter referred to as "leg pain")
  - Participants with leg pain persisting for at least 3 months and with small change in the pain for at least 4 weeks
  - Participants with leg pain of at least one side which was more severe than low back pain
  - Participants with no specific diseases in the lower back (eg, tumor or spondylitis)
- Participants whose pain intensity of leg pain and low back pain satisfied all of the following:
  - Average daily pain intensity of ≥ 4 for leg and low back pain at Visit 1

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– The weekly mean of average daily pain intensity of leg and low back pain over the last 7 days at Visit 2 (including Visit 2 [Day 1]) was ≥ 4 to < 10

2. Exclusion criteria

- Participants whose primary pain was determined to be located in areas other than the lower back or legs or participants who have neuropathic pain in areas other than the lower back or legs
- Participants with osteoarthritis (hip or knee), fresh fracture due to osteoporosis, rheumatoid arthritis, or arteriosclerosis obliterans requiring treatment
- Participants with major depression, bipolar disorder, schizoaffective disorder, cognitive impairment, other psychiatric diseases, or psychiatric symptoms that were considered inappropriate by the investigator/subinvestigator, or those with a past history of these diseases
- Participants with the following uncontrolled diseases: thyroid dysfunction, convulsive disorder such as epilepsy, or Sjogren's syndrome
- Participants with difficulty in walking by themselves or with a high risk of falling
- Participants with spinal stenosis of cauda equina disorder type according to the symptom classification
- Participants with a PHQ-9 score of ≥ 15
- Participants with a history of hip surgery
- Participants who could not discontinue the prohibited concomitant drugs or therapies at Visit 1, or those who had to use the prohibited concomitant drugs including analgesics or prohibited concomitant therapies during the study
- Participants who had received epidural injection, facet block, nerve block, tender point injection, or other invasive therapy for the relief of low back pain within 30 days prior to Visit 1.
- Participants who had used prohibited concomitant drugs, including analgesics, for the relief of low back pain or had received prohibited therapies within 10 days prior to Visit 2

Test Product, Dose and Mode of Administration, Lot Number:

- S-637880 tablets 5 mg ([redacted])

Four tablets per dose were orally administered twice daily in the morning and evening.

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Duration of Treatment:
Eight weeks

Reference Therapy, Dose and Mode of Administration, Lot Number:

- S-637880 tablets Placebo-B ([redacted])

Four tablets per dose were orally administered twice daily in the morning and evening.

Criteria for Evaluation:

Efficacy Assessment:

Efficacy was assessed with respect to the following scales:

- NRS (pain intensity)
  The maximum daily pain intensity and average daily pain intensity on the NRS for leg pain and low back pain, ie, NRS scores of worst/average daily leg pain and low back pain
- NPSI
- PGI-I
- CGI-S
- ODI
- SF-36
- EQ-5D-5L
  A descriptive questionnaire and the European Quality of Life Visual Analog Scale (EQ VAS) score
- MOS-SS-R
- PDQ-5
- PHQ-9
- Percentage of participants who received rescue medication

Safety Assessment:

Safety was assessed through physical examinations, vital signs, ECG, laboratory assessments, and C-SSRS. All AEs/SAEs were collected from the date of signing of the informed consent form (ICF) through the end of follow-up period. The severity and seriousness of an event was determined by the investigator/subinvestigator according to the protocol-specified definitions. The relationship of an event to the study intervention was determined by the investigator/subinvestigator. An AESI was defined as an AE related to the skin (except when the investigator could clearly rule

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out drug eruption [eg, insect bite, trauma]). If an AESI occurred between the start of study intervention and the end of Follow-up Period, the investigator/subinvestigator was to collect information on the AE.

C-SSRS is a rating scale consisting of a maximum of 19 items for the occurrence, severity, and frequency of suicidal ideation.

PK Assessment:

The investigator or his/her designee collected blood samples for the measurement of plasma concentrations of S-637880 and S-637880 demethyl at Visit 4, Visit 5, and Visit 7 (or at discontinuation).

Statistical Methods:

Efficacy Analyses:

All efficacy analyses were performed for the ITT population. And for primary analysis of the primary endpoint, the same analysis was performed also for the PPS.

Primary Endpoint

The primary endpoint was the change from baseline in the mean weekly NRS score of worst leg pain after 8 weeks of treatment.

For the primary analysis, the mean weekly NRS score of worst daily leg pain at Weeks 1 to 9 and its change from baseline were summarized by intervention group. A Mixed-effects model for repeated measures (MMRM) with an unstructured covariance structure was used to estimate intervention group difference between S-637880 and placebo with change from baseline. The model included intervention group, time point (Weeks 1 to 8), interaction between intervention group and time point as fixed effects, and baseline score, painDETECT score (< 13, ≥ 13) at the randomization, and type of disease (specific chronic low back pain, nonspecific chronic low back pain) as covariates. The Kenward-Roger method was used for adjusting degrees of freedom.

For supplementary analyses, an analysis of covariance (ANCOVA) with single imputation and a tipping point analysis were performed.

Secondary Endpoints

1. Change from baseline in the mean weekly NRS score
   The following mean weekly NRS scores at Weeks 1 to 9 and their changes from baseline were summarized by intervention group.
   - Mean weekly NRS score of average daily leg pain
   - Mean weekly NRS score of worst daily low back pain

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- Mean weekly NRS score of average daily low back pain

A MMRM model was used as with the primary analysis for the primary endpoint.

2. Time to 30% or 50% improvement in the mean weekly NRS score
   A Kaplan-Meier curve was plotted for the following endpoints. Non-improvement participants were treated as censored cases.
   - Time to 30% or 50% improvement in the mean weekly NRS score of worst daily low back pain
   - Time to 30% or 50% improvement in the mean weekly NRS score of average daily low back pain
   - Time to 30% or 50% improvement in the mean weekly NRS score of worst daily leg pain
   - Time to 30% or 50% improvement in the mean weekly NRS score of average daily leg pain
3. Change from baseline in NPSI Score
   The NPSI scores (total score, sub scores [burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia]) at each visit from Visit 2 to Visit 8 and their changes from baseline were summarized by intervention group.

   A MMRM model was used as with the primary analysis for the primary endpoint.
4. PGI-I Score
   The PGI-I score at each visit from Visit 3 to Visit 8 was summarized by intervention group.
   A MMRM with an unstructured covariance structure was used with PGI-I score as the response variable, intervention group, time point (Visit 3 to Visit 7), interaction between intervention group and time point as fixed effects, painDETECT score (< 13, ≥ 13) at the randomization, disease (chronic low back pain except nonspecific type, chronic nonspecific low back pain) as covariates. The Kenward-Roger method was used for adjusting degrees of freedom.
5. Change from baseline in CGI-S Score
   The CGI-S score at each visit from Visit 2 to Visit 8 and its change from baseline were summarized by intervention group. A MMRM model was used as with the primary analysis for the primary endpoint.
6. Change from baseline in ODI Score
   The ODI score at Visit 2, Visit 5, and Visit 7, and its change from baseline were

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summarized by intervention group. A MMRM model was used as with the primary analysis for the primary endpoint.

7. Change from baseline in SF-36 Score
   The SF-36 scores (3 summary scores and 8 subscale scores) at Visit 2, Visit 5, and Visit 7, and their changes from baseline were summarized by intervention group.
   A MMRM model was used as with the primary analysis for the primary endpoint.
8. Change from baseline in EQ-5D-5L Score
   The EQ-5D-5L scores (EQ-5D descriptive system and EQ VAS) at Visit 2, Visit 5, and Visit 7, and their changes from baseline were summarized by intervention group. A MMRM model was used as with the primary analysis for the primary endpoint.
9. Change from baseline in PHQ-9 Total Score
   The PHQ-9 total score at Visit 2, Visit 5, Visit 7, and Visit 8, and its change from baseline were summarized by intervention group. A MMRM model was used as with the primary analysis for the primary endpoint.
10. Change from baseline in MOS-SS-R Score
    The MOS-SS-R score at Visit 2, Visit 5, and Visit 7, and its change from baseline were summarized by intervention group. A MMRM model was used as with the primary analysis for the primary endpoint.
11. Change from baseline in PDQ-5 Total Score
    The PDQ-5 total score is the sum of each question score which range from 0 to 4, thus the total score can range from 0 to 20.
    The PDQ-5 score at Visit 2, Visit 7 and its change from baseline were summarized by intervention group. For participants who discontinued early, the value at Visit of discontinuation was used.
    An ANCOVA was used in order to compare S-637880 and placebo; the model included the following: change from baseline as the response variable, intervention group as a fixed effect, baseline score, painDETECT score (< 13, ≥ 13) at the randomization, and type of disease (chronic low back pain except nonspecific type, chronic nonspecific low back pain) as covariates.
12. Percentage of participants who received rescue medicines
    The percentage of participants who received rescue medicines at least once between Visit 1 and the end of the study was presented for each intervention group.

Safety Analyses:

AEs were classified by the system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1.

The overall number of participants with a treatment-emergent adverse event (TEAE), death, serious TEAE other than death, and TEAE leading to discontinuation of study intervention and their percentages were counted for each intervention group. The Clopper-Pearson method was used to calculate the confidence interval (CI) of percentages in the analyses of AEs. The number of reported TEAEs was also presented. AEs occurring in 5% or more in either intervention group were summarized by PT for each intervention group. Treatment-related TEAEs were summarized in the same manner as TEAEs. In addition, the summary was presented by severity, outcome, and time of onset. Treatment-related TEAEs also were summarized in the same manner. The number of participants with an AESI (skin-related AEs) and their percentages were also presented.

For blood pressure/pulse rate, summary statistics of measurement values and changes from baseline in systolic and diastolic blood pressure and pulse rate were calculated by intervention group for each time point.

For laboratory values, summary statistics of measurement values and change from baseline in laboratory test data were calculated by intervention group for each time point. Qualitative urinalysis parameters were summarized by intervention group for each time point by using the frequency count and the percentage of participants in each category.

For 12-lead ECG, interpretations (normal, abnormal-not clinically significant, abnormal-clinically significant) were summarized by intervention group for each time point by using the frequency count and the percentage of participants in each category.

For C-SSRS, the distribution of the presence/absence of suicidal ideation and suicidal behavior was summarized by intervention group.

PK Analyses:

Plasma Concentrations

Individual plasma concentrations of S-637880 and its metabolite, S-637880 demethyl, were listed and graphed against the elapsed time from the last administration.

PK Parameters

Plasma trough concentrations (C_{trough}) defined as the plasma concentrations of S-637880 and S-637880 demethyl between 10 and 14 hours after administration. C_{trough} was summarized by time point with N, Mean, standard deviation (SD), coefficient of variation (CV%, calculated by SD/Mean × 100), Geometric Mean, CV% Geometric Mean, median, minimum, and maximum values.

Summary of Results:

This study was prematurely terminated at all study sites in accordance with the [redacted] recommendation issued on the basis of a treatment-related SAE (agranulocytosis) and a treatment-related TEAE (white blood cell count decreased) reported in 1 participant each in the S-637880 group in this

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study. A total of 51 participants had been randomized at termination versus planned 160 participants.

Efficacy:

Primary Endpoint

For the ITT population, the mean (SD) weekly NRS score of worst daily leg pain at baseline was 7.022 (0.925) in the S-637880 group and 6.761 (1.124) in the placebo group. The mean (SD) weekly NRS score of worst daily leg pain at Week 8 was 5.395 (2.062) and 5.527 (2.174), respectively, and the mean (SD) change in the mean weekly NRS score of worst daily leg pain at Week 8 from baseline was −1.692 (1.863) and −1.458 (1.903), respectively.

The MMRM analysis showed that the adjusted mean (standard error [SE]) change in the mean weekly NRS score of worst daily leg pain at Week 8 from baseline was −1.539 (0.373) and −1.343 (0.365), respectively. The difference in the adjusted mean changes from baseline in the mean weekly NRS score of worst daily leg pain between two groups (S-637880 − placebo) was −0.196 (95% CI, −1.193 to 0.800), meaning that the difference of decreases in NRS score was not statistically significant between two groups (p = 0.6934).

Secondary Endpoints

The secondary efficacy endpoints were the change in the mean weekly NRS score (average daily leg pain and worst daily/average daily low back pain) at Week 8 from baseline, the time to 30% or 50% improvement in the mean weekly NRS score, the change from baseline in NPSI score, PGI-I score, the change from baseline in CGI-S score, the change from baseline in ODI score, the change from baseline in SF-36 scores, the change from baseline in EQ-5D-5L scores, the change from baseline in PHQ-9 score, the change from baseline in MOS-SS-R score, the change from baseline in PDQ-5 score, and the percentage of participants who received rescue medication. No statistically significant improvements in any of the secondary endpoints were seen in the S-637880 group compared to the placebo group.

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Safety:

A total of 13 TEAEs were reported in 6 of 25 participants of the S-637880 group (24.0%), while 6 TEAEs were reported in 4 of 26 participants of the placebo group (15.4%). Of these TEAEs, 2 TEAEs (agranulocytosis and white blood cell count decreased) reported in 2 of 25 participants of the S-637880 group (8.0%) and 2 TEAEs (blood glucose increased and urinary occult blood positive) reported in 1 of 26 participants of the placebo group (3.8%) were considered related to the study intervention.

Two severe TEAEs (agranulocytosis and cytokine storm) were reported in 1 of 25 participants of the S-637880 group (4.0%). Both events were resolved. One of the TEAEs (agranulocytosis) was a SAE and considered related to the study intervention, and the other TEAE (cytokine storm) was considered unrelated to the study intervention. The agranulocytosis occurred 33 days after the initial dose of study intervention. The participant discontinued the study intervention 37 days after the initial dose of study intervention and recovered from the event 25 days from the onset following hospitalization and medication. All TEAEs except for two TEAEs were mild or moderate in severity. All treatment-related TEAEs were resolved.

No deaths were reported during the study. One nonfatal serious TEAE (agranulocytosis) was reported in 1 of 25 participants in the S-637880 group (4.0%). No nonfatal serious TEAEs were reported in the placebo group.

Three TEAEs led to discontinuation of study intervention in 2 of 25 participants in the S-637880 group (8.0%): agranulocytosis reported in 1 participant and considered related to the study intervention; alanine aminotransferase and aspartate aminotransferase increased reported in another participant and considered unrelated to the study intervention.

One AESI (TEAE related to the skin) was reported in 1 of 25 participants in the S-637880 group (4.0%). The event was considered unrelated to the study intervention by the investigator. The event occurred 1 day after the last administration of S-637880 (44 days after the initial dose), was mild in severity and resolved without treatment. No AEs related the skin were reported in the placebo group.

No study intervention-related and clinically significant trends were identified in laboratory parameters (hematology, blood chemistry, and urinalysis), vital signs (blood pressure and pulse rate), 12-lead ECGs, C-SSRS, or other safety observations, although treatment-related TEAEs (agranulocytosis and white blood cell count decreased) were reported in 1 participant each in the S-637880 group.

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PK:

A total of 168 plasma concentration data from 25 participants were obtained for S-637880 and S-637880 demethyl (84 concentration data for each analyte). The descriptive statistics of C_{trough} of S-637880 were not calculated because the data were obtained in less than 3 participants.

CONCLUSIONS

Efficacy Conclusions:

No improvement from baseline in the primary endpoint of the mean weekly NRS score of worst daily leg pain at Week 8 was found in the S-637880 group compared to the placebo group; the difference between two groups was not statistically significant. No statistically significant improvements in any of the secondary endpoints were seen in the S-637880 group compared to the placebo group.

Safety Conclusions:

This study was prematurely terminated at all study sites in accordance with the [redacted] recommendation issued on the basis of a treatment-related SAE (agranulocytosis) and a treatment-related TEAE (white blood cell count decreased) reported in 1 participant each in the S-637880 group. Except for the TEAEs, no clinically significant trends were identified during this study.

PK Conclusions:

A total of 168 plasma concentration data from 25 participants were obtained for S-637880 and S-637880 demethyl (84 concentration data for each analyte). The descriptive statistics of C_{trough} of S-637880 were not calculated because the data were obtained in less than 3 participants.

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