Supplementary Online Content

Guo X, Zhang T, Yuan G, et al. GABA analogue HSK16149 in Chinese patients with diabetic peripheral neuropathic pain: a phase 3 randomized clinical trial. *JAMA Netw Open*. 2024;7(8):e2425614. doi:10.1001/jamanetworkopen.2024.25614

eTable 17. Summary of Treatment-Period Adverse Events With a Combined Incidence of ≥1.0% by SOC and PT-SS

eTable 18. Summary of Treatment-Phase Adverse Events With a Combined Incidence of ≥1.0% by SOC and PT and Associated With the Investigational Drug-SS

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Study Design

Overall design

This study uses an adaptive design to seamlessly link Phase II and Phase III together. The study consists of two stages, with the first stage designed to initially assess the efficacy and safety of different doses of HSK16149 for the treatment of DPNP and recommend the optimal dose of HSK16149 that is safe and effective to enter the second stage study. The second stage of the study was designed to confirm the efficacy and safety of the recommended dose of HSK16149 for DPNP in the first phase. Overall design is shown in **Figure 1**.

In the first stage, enrolled subjects were randomized in a 1:1:1:1:1:1 ratio to receive HSK16149 40 mg/day [20 mg twice daily (BID)], 80 mg/day (40 mg BID), 120 mg/day (60 mg BID), 160 mg/day (80 mg BID), placebo (BID), and pregabalin 300 mg/day (150 mg BID) treatment. An interim analysis of safety and efficacy were conducted by an independent statistician after approximately 360 subjects had completed 5 weeks of study treatment. The results were submitted for review to the Independent Data Monitoring Committee (IDMC) established for this study, which recommended to the sponsor, based on the results of the safety and efficacy analysis that included (1) whether the results of the interim analysis support study entry into stage II and (2) the recommended dose of HSK16149 for stage I of the study. Stage I enrollment continued during the interim analysis, and enrolled subjects continued to receive study treatment in their assigned and complete safety follow-up at day 7 after the final trial drug administration. The sponsor and study team, investigators, and subjects remained blinded throughout the study period.

In the second stage, following the completion of the interim analysis, the sponsor referred to the IDMC recommendations to determine the HSK16149 treatment dose for the stage II study (preliminary estimate of two doses) and initiated stage II enrollment. Subjects were randomized to receive either one of the HSK16149 doses or placebo on a 1:1:1 basis. At the same time, enrollment in the stage I study was discontinued and enrolled subjects continued to receive study treatment in their assigned and complete a safety follow-up visit on day 7 after the final trial drug administration. When the number of cases in the stage II reached a percentage of the estimated sample size (e.g., reaches 50% of the estimated sample size), the stage II study sample size were recalculated by an independent statistician and IDMC advised

the sponsor to make adjustments to the total study sample size when applicable.
At the end of the study, data from the same treatment of subjects were pooled for final efficacy and safety analysis.

Study Treatment and Follow-Up

After signing the informed consent form (ICF), we enter the screening period. Subjects who complete the screening tests specified in the protocol during the screening period and meet the inclusion and non-exclusion criteria enter the placebo introduction period, during which they are required to take placebo once daily in the morning and once daily in the evening (Phase I: 6 capsules/dose, BID; Phase II: 4 capsules/dose, BID) for 1 week. Subjects were assessed at baseline (D0) on randomization criteria and those who qualified were randomized to each group. Stratified randomization was used, i.e., placebo introduction period 1-week ADPS as baseline value, stratified by ADPS < 6 and ≥ 6 scores.

The drug treatment period, including a titration period of 1 week (stage I: titration dose of HSK16149 40 mg BID for both the 120 mg/day and 160 mg/day dose groups of HSK16149, and titration dose of pregabalin 75 mg BID for the 300 mg/day dose group of pregabalin, with no change in dose for other dose groups; stage II includes two predicted HSK16149 dose group and one placebo group (HSK16149 dose was determined as HSK16149 40 mg and HSK16149 80 mg based on the results of the mid-term analysis). After titration was completed, subjects received a further 12 weeks of fixed-dose treatment with the experimental drug at the set dose for each dose group. After completion of fixed-dose treatment, subjects received a safety follow-up on day 7 after the final trial drug administration. For subjects who do not complete 13 weeks of treatment, an early termination visit must be completed.

During this study, if a subject experiences intolerable pain, he or she is required to contact the investigator as soon as possible. Upon confirmation by the investigator, acetaminophen tablets, which is a remedial drug uniformly provided in this study, may be administered. The dosages of acetaminophen tablets are 0.5 g/dose every 4 to 6 h. The maximum daily dose should not exceed 2.0 g and should not be taken for more than 5 consecutive days.

Discussion of study design, including the selection of control group

The aim of this study was to evaluate the efficacy and safety of HSK16149 treatment in Chinese DPNP subjects at different doses of administration. Based on the pharmacological mechanism of action of HSK16149 and the results of existing studies, the results of similar drugs, including the study of

mirogabalin, which has similar mechanism of action characteristics to HSK16149, were analyzed and incorporated into the adaptive design concept. The optimal dose of HSK16149 was recommended to enter the second stage of the study to evaluate the efficacy and safety of different doses of HSK16149 administered compared to placebo for the treatment of DPNP and to steadily accelerate the clinical development of HSK16149.

To achieve an adaptive design and to ensure that the entire study was conducted in a blinded manner, an independent statistician was responsible for processing and analyzing the data for the midterm analysis in a non-blinded manner. The study completed the enrollment program in stage I, i.e., 60 subjects were enrolled in each dose group, for a total of approximately 360 subjects in 6 dose groups, and the stage I interim analysis was conducted after the last subject completed 5 weeks of treatment with the experimental drug. The stage II interim analysis was conducted when the number of subjects who had completed the 13-week visit in stage II reached approximately 50% of the estimated sample size. To objectively assess the data from the interim analysis, an IDMC was established to review the safety and efficacy data from the interim analysis with the assistance of an independent statistician to recommend the optimal dose of HSK16149 for safe and effective entry into the second phase of the study. The interim analysis did not affect the stage I study enrollment and the process by which subjects received study treatment and follow-up to support the final pooled analysis of data from both stages of the study.

Based on the pathogenesis and clinical characteristics of DPNP and with reference to FDA and EMA guidelines for clinical studies of drugs for the treatment of pain, this study was designed for superiority over placebo control. Stage I subjects were randomized in equal proportions to different dose groups of HSK16149, the pregabalin group, and the placebo group. Stage II subjects were randomized in equal proportions to the HSK16149 different dose group, and the placebo group.

According to the EMA guidelines it is recommended that the treatment duration for a fixed dose administration period should be 12 weeks or longer, with a 1-week dose titration considered for the higher dose group. Therefore, the duration of fixed-dose treatment in this study was 12 or 13 weeks. Considering the characteristics of pain clinical trials, especially the high placebo effect in the Asian subject population, a 1-week placebo introduction period was established to reduce the potential impact of previous analgesics on the assessment of efficacy of the drugs used in this trial and to minimize the placebo effect. To ensure the safety of the study medication, subjects in the HSK16149 120 mg/day and 160 mg/day dose groups and the pregabalin 300 mg/day dose group received a 1-week titration of the investigational

drug prior to entering the fixed dose treatment period. The titration dose was HSK16149 40 mg BID for both the 120 mg/day and 160 mg/day dose groups of HSK16149, and 75 mg BID for the 300 mg/day dose group of pregabalin, with no change in dose for the other dose groups. All subjects then entered a 12-week fixed-dose treatment period.

The basis for the diagnosis of diabetes and DPNP, the level of glycemic control, and the severity of pain in the study population were specified in the enrollment criteria. To minimize the degree of subject response to placebo, patients with moderate or severe pain DPNP were enrolled, and pain intensity was measured using both the visual analog scale (VAS) and the numeric rating scale (NRS) to improve score representativeness. Among them, the VAS reflects the average pain level of the subjects at baseline (past 24 h); the ADPS (i.e., average daily NRS over the previous 7 days) is suitable to represent the overall pain severity of the subjects at baseline. Both scores resulted in moderate to severe pain before enrollment, and VAS ≥ 90 mm or ADPS ≥ 9 points were excluded to ensure subject safety. In addition, other diseases causing peripheral neuropathic pain and other underlying diseases that may pose a potential risk to the safety of the subjects were excluded, and the use of recent analgesics and strong analgesics for pain relief was limited to minimize subjective bias in the assessment of effectiveness, such as the subject's memory of previous efficacy.

Based on the above design considerations, the primary efficacy end point of the study was determined to be the change in ADPS from baseline at 5 weeks of trial drug treatment and the secondary efficacy end point of ADPS response rate in Phase I. The primary efficacy end point in Phase II was the change in ADPS from baseline at 13 weeks of trial drug treatment. In addition, a series of secondary efficacy end points were established in Phase 2, including change from baseline in ADPS per week during study treatment; proportion of subjects with ADPS response rates (≥ 30% and ≥ 50% decrease in ADPS from baseline) at 13 weeks of trial drug treatment; change from baseline in VAS scores at 13 weeks of trial drug treatment; and change from baseline in average daily sleep disturbance score (ADSIS) at 13 weeks of trial drug treatment. (ADSIS) from baseline at 13 weeks of treatment; change from baseline in the Short Form McGill Pain Questionnaire (SF-MPQ) score at 13 weeks of treatment; change from baseline in the five-level version of the European Five Dimensional Health Inventory (EQ-5D-5L) score at 13 weeks of treatment; and the patient's impression of overall change in pain (PGIC) score at 13 weeks of treatment. The change from baseline in ADPS at 5 weeks of treatment with the experimental drug was used as a surrogate end point in the interim analysis, which was expected to better predict the outcome

of the primary efficacy end point at the final analysis of the study to support the decision making in the second phase of the study, taking into account the characteristics of post-treatment pain scores over time in the pivotal study of similar drugs.

Subjects' treatment group assignment method

Randomization in this study was performed using the Interactive Response Technology (IRT) system, which automatically randomized treatment groups according to randomization numbers based on the principle of zone group randomization. According to the randomization assignment plan, in the first phase of the study, eligible subjects were randomized in a 1:1:1:1:1:1 ratio according to central randomization to HSK16149 40 mg/day (20 mg BID), 80 mg/day (40 mg BID), 120 mg/day (60 mg BID), 160 mg/day (80 mg BID), placebo (BID), or pregabalin's 300 mg/day (150 mg BID) group. Stratified randomization was performed based on baseline ADPS scores (< 6 and ≥ 6). In the second phase of the study, eligible subjects were randomized centrally in a 1:1:1 ratio to HSK16149 40 mg/day (20 mg BID), HSK16149 80 mg/day (40 mg BID), and placebo (BID) according to the IDMC meeting resolution. Stratified randomization was performed according to baseline ADPS scores (< 6 and ≥ 6).

Dose selection in the study

Doses retained for stage II were determined based on risk-benefit assessment from the four available validated HSK16149 doses based on stage I data. The primary end point for the mid-period analysis is the change in ADPS values at week 5 relative to baseline. As planned, the midterm analysis will collect ADPS data from 360 subjects at week 5, with approximately 60 subjects in each group. The best dose group will be selected by the midterm analysis to proceed to the next phase of the clinical trial. Designate E_1, E_2, E_3, and E_4 as the 4 HSK16149 dose groups and P as the placebo control group. Assume that θ_i is the drug effect (change in ADPS from baseline to week 5) of the dose group E_i of HSK16149 compared to placebo as calculated by the mid-period analysis. The test statistic was calculated for each dose group versus the placebo group by pairwise comparison of the four dose groups with placebo, and the two dose groups with the largest values based on the value of the test statistic were selected as the doses for the stage II study.

Blinding

This study is a double-blind design. Subjects and all personnel involved in study operations, including investigators, study center personnel and sponsors, and CRO personnel, should be blinded throughout the study period. During the interim analysis, only independent statisticians will have access to the blinded bottom of the experimental drug to support the unblinded data analysis. The unblinded statistical team will submit the results of the unblinded data analysis to the IDMC for review. Unless there is an emergency, trial drug codes will be provided only after study completion and clinical database lock.

Emergency unblinding was performed through the IRT system. Blinding is not permitted in the study except in the event of an emergency (e.g., SAE) where the subject's randomization code is known to potentially affect treatment. If possible, prior to unblinding, the investigator should consult with the medical monitor of the study and/or the sponsor's responsible personnel to determine if unblinding is necessary. Once a subject's study medication status has been unblinded on an emergency basis, the subject should be treated as an early withdrawal from study treatment and the investigator should keep detailed records of the date, time and reason for unblinding.

eMethods 2. Selection of Study Population

Inclusion criteria

Subjects who meet all of the following criteria may be enrolled in this study.

1. Able to understand and voluntarily sign a written ICF

2. Male or female aged 18 to 75 years (including the threshold).

3. Meet the diagnosis of DPNP and have had diabetic peripheral neuropathy (DPN) pain for ≥ 6 months; the diagnosis of DPNP is subject to both.

1) A definite history of diabetes mellitus.

2) Neuropathy presenting at or after the diagnosis of diabetes mellitus.

3) Clinical signs and symptoms consistent with the presentation of DPN.

4) Abnormalities in any 1 of the 5 tests (ankle reflex, vibration sensation, temperature sensation, pinprick pain sensation, pressure sensation) in those with clinical symptoms.

4. Stable glycemic control within 3 months prior to screening, i.e., HbA1c ≤ 9.0% at screening. Stable treatment with glucose-lowering drugs for at least 30 days at the time of screening, and the glucose-lowering regimen is expected to remain unchanged throughout the study.

5. Mean pain VAS score ≥ 40 mm and < 90 mm in the past 24 h assessed at screening.

Exclusion Criteria

Subjects meeting any of the following criteria were excluded from enrollment in this study.

1. The presence of peripheral neuropathy or pain unrelated to DPN (including but not limited to that caused by cerebrovascular disease, Guillain-Barre syndrome, cervical and lumbar spine disease, osteoarthritic or tendinopathy, chronic kidney disease or uremia, thyroid disease, intracranial tumors, trauma, etc.) that may confound the assessment of DPNP

2. The presence of conditions that, in the opinion of the investigator, may affect the assessment of pain, such as skin disease in the involved skin area and which may affect sensation.

3 Have a chronic systemic disease that the investigator assesses may affect the subject's participation in the study, including but not limited to.

1) Having severe cardiopulmonary disease such as unstable angina, myocardial infarction, severe arrhythmias, WHO cardiac function class III to IV at screening, hypertension that is poorly controlled despite aggressive treatment, systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening; recurrent asthma attacks, etc.

2) Presence of chronic digestive system diseases, such as liver diseases like liver fibrosis, recurrent episodes of dyspepsia or diarrhea, peptic ulcers

3) Presence of neuropsychiatric disorders that, in the opinion of the investigator, may affect the evaluation for DPNP or affect the self-rating, including epilepsy, recurrent episodes of dizziness, headache, memory and cognitive impairment; cerebrovascular accident (e.g., cerebral infarction) or transient ischemic attack within 6 months prior to screening

4) History of malignancy (excluding cured basal cell carcinoma of the skin, carcinoma in situ and papillary thyroid cancer) or history of antineoplastic therapy within 5 years prior to screening.

4. Severe hematologic, hepatic, or renal function abnormalities consistent with any one of the following clinical laboratory test results.

1) Hematology: neutrophils < 1.5 × 109/L, or platelets < 90 × 109/L, or hemoglobin < 100 g/L.

2) Liver function: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN); or total bilirubin (TBIL) > 1.5 × ULN.

3) Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2 (calculated according to the simplified MDRD formula).

4) Creatine kinase > 2.0 × ULN.

5. Known history of substance abuse and/or alcohol abuse [more than 14 servings of alcohol per week (1 serving equivalent to 360 mL of beer, or 45 mL of spirits with 40% alcohol content, or 150 mL of wine)].

6. History of acute complications of diabetes such as diabetic ketoacidosis, hyperglycemic hyperosmolar state, or lactic acidosis within 6 months prior to screening

7. Subjects with any active infection at the time of screening and who, in the opinion of the investigator, are not suitable for inclusion.

8. Positive hepatitis B surface antigen (HBsAg) or positive hepatitis C virus antibody (HCV Ab) at screening [subject to further testing by hepatitis B virus deoxyribonucleic acid (HBV DNA) titer or

hepatitis C virus ribonucleic acid (HCV RNA) test (exceeding the lower limit of detection of the assay requires exclusion)], positive human immunodeficiency virus antibody (HIV Ab), positive serum syphilis spirochete (further check for syphilis spirochete titer is required and should be excluded if positive).

9. Use of a prohibited drug prior to screening (see Section 6.3 of the study protocol) or a change in a combination of restricted drugs within 30 days prior to screening; if the subject is using a prohibited drug prior to screening, the drug must be discontinued for at least 5 half-lives (as indicated) prior to the screening visit before screening can proceed and the drug must be discontinued for the duration of the study.

10. Prior use of pregabalin ≥ 300 mg/day or gabapentin ≥ 1200 mg/day with a claimed lack of clinical efficacy.

11. Known history of hypersensitivity to the experimental drug or remedial drug component or other chemically structured similar drugs or excipients

12. Prior history of suicidal behavior or suicidal ideation.

13. Women who are pregnant, preparing to become pregnant during the study period, or are breastfeeding; subjects who do not wish to use reliable contraception (including condoms, spermicides, or IUDs, etc.) between the start of signing the ICF and 28 days after the last trial drug administration, or women who plan to use progesterone-containing contraceptives during this period.

14. have participated in any other clinical study within 30 days prior to screening

15. Other circumstances exist that, in the judgment of the investigator, preclude compliance with the protocol to complete the study.

16. Other circumstances that, in the judgment of the investigator, may compromise the safety of the subject by participating in this study.

Random criteria

Any of the following criteria need to be met before entering the titration period after completion of the introductory period.

1. All inclusion criteria are met and none of the exclusion criteria are met.

2. Pain VAS score ≥ 40 mm and < 90 mm at the introductory period and baseline visit

3. A daily pain NRS score of ≥ 4 and < 9 during the 1-week introductory period and at least 4 days of pain NRS assessment completed.

4. Trial drug compliance of 80-120% during the introductory period.

Early Withdrawal from Study Treatment

Subjects may decide to terminate study treatment early at any time during the study without prejudice to the continuation of appropriate clinical care. The investigator should arrange for the subject to terminate study treatment early and complete an end-of-study treatment (EOT) visit assessment if possible if one of the following conditions occurs

1. Subjects are found to be enrolled in the study in violation of the enrollment criteria and the investigator determines that the safety of the subject is compromised.

2. Subject withdraws consent.

3. Insufficient efficacy and, in the judgment of the investigator, other medications are required to treat DPNP.

4. Subject is judged by the investigator to be unfit for further study treatment due to AE.

5. Lose blinding of the study drug.

6. Pregnancy.

7. Significant noncompliance with the protocol-defined process including study treatment and, in the judgment of the investigator, affects safety assessment or efficacy analysis.

8. Subject withdraws consent.

9. Loss of visit.

10. Death.

eMethods 3. Statistical Analysis Plan

Analysis set

Full analysis set (FAS): includes all subjects who were randomized in groups, treated with at least one trial drug and had at least 1 post-baseline efficacy evaluation according to the intent-to-treat (ITT) principle.

Protocol-compliant analysis set (PPS): all subjects in the FAS with good compliance during the study, complete data on key efficacy indicators, and no significant study protocol deviations.

Safety analysis set (SS): all subjects who received at least one trial drug after randomization and for whom post-administration safety evaluation data were available.

General principles

SAS version 9.4 was used for the statistical analysis of this study. Descriptive statistical analyses were performed according to the following principles unless otherwise stated: means, standard deviations (SD are listed for measurement data, and frequencies (percentages) are listed for count and rank data.

The number of decimal places for the minimum and maximum values is consistent with the original data recorded in the database unless otherwise stated. The mean and median are retained in one more decimal place than the original data recorded in the database, and the standard deviation is retained in two more decimal places than the original data recorded in the database. The number of decimal places for all statistics does not exceed four.

For categorical indicators, descriptive statistics include the number of examples and percentages. The number of cases is a whole number; percentages are retained to one decimal place, and percentages are not reported for frequencies of 0.

P-values greater than or equal to 0.0001 in statistical tests were retained to four decimal places, and P-values less than 0.0001 were indicated by "<.0001."

Multiple testing

Because this trial included analysis of the first stage of dose selection (HSK16149 40 mg group, 80 mg group, 120 mg group, and 160 mg group option two) and combining data from both stages (second stage randomization of additional subjects to the HSK16149 selected dose group versus the placebo group), in

order to be able to keep the overall type I error rate below $\alpha = 0.05$, the method proposed by Friede et al. in 2011 was used to test whether the HSK16149 selected dose group was superior to the placebo group in terms of key efficacy measures. The method of Friede et al. includes many-to-one comparisons, closed testing procedure and the combination test method.

Missing data handling

Efficacy-based data: any missing values will not be filled except for the primary effectiveness end point for which they will be filled. Subjects will be required to complete at least 4 days of daily pain scores to calculate the one-week ADPS; if a subject does not complete 4 days of daily pain scores in a week, the ADPS data for that week will be missing and the missing data will be filled.

The primary analysis of the validity end points in this study will use the Markov chain Monte Carlo method (MCMC method) of the multiple fill (MI) method to fill the missing data under the assumption that the data are missing at random, the missing data pattern is arbitrary, and they follow a multivariate normal distribution. The application will use mcmc in SAS Procmi, using the subject's weekly ADPS as the variable. The SAS procmi process will generate 10 filler datasets using the seed number of 0510 and 10 filler datasets, and then calculate the test statistic for each filler dataset based on the description of the primary efficacy end point analysis by statistical analysis, and then synthesize the calculated results for each filler dataset by the SAS procmianalyze process to finally determine the test results.

According to the protocol, if a subject experiences intolerable pain, he or she is required to take acetaminophen tablets, a remedial drug provided uniformly in this study, after confirming with the investigator. When the subject used the remedial drug on the same day, the possible effect of the supplemental drug use on the subject's pain score needs to be considered. Subjects experiencing intolerable pain, i.e., considering that the subject's use of remedial medication on that day was in a poor pain situation, were chosen to compare the pain score on that day with the subject's baseline maximum pain score, and the greater value will be used as the pain score on that day for the calculation of ADPS for that week.

As for safety data, if not specified, missing data are not filled in, but only when the summary analysis needs to be divided into time to fill in the summary calculation of missing data.

Efficacy end point analysis

For primary efficacy end point analysis, the FAS set was used as a sensitivity analysis for the change from baseline in ADPS at week 13 for the primary efficacy indicator. If the results in the two datasets are inconsistent they will be discussed in the statistical analysis report. The method proposed by Friede et al. in 2011 was used to test whether the HSK16149 selected dose group was superior to the control drug group on the primary efficacy measure (change from baseline in ADPS at week 13) at a one-sided significance level of $\alpha = 0.025$.

The secondary efficacy end point analysis was based on the FAS set. Secondary efficacy end points included the following: 1) ADPS response rate (proportion of subjects with ≥ 30%, ≥ 50% decrease in ADPS from baseline) at 5 weeks, 13 weeks of treatment with the trial drug; 2) Change from baseline in VAS scores at 13 weeks of treatment with the trial drug; 3) Comparison of change from baseline in weekly ADPS between HSK16149 and placebo at weeks 1 to 13; 4) Change from baseline in ADSIS at 13 weeks of trial drug treatment; 5) Change from baseline in SF-MPQ scores at 13 weeks of trial drug treatment; 6) PGIC scores at 13 weeks of trial drug treatment; 7) Change from baseline in EQ-5D-5L at 13 weeks of trial drug treatment. All secondary efficacy metrics will be tested for differences in efficacy between the two selected trial groups and the placebo group using the Bonferroni correction (one - sided 0.0125 significance level).

Change from baseline in ADPS

For the secondary end point indicator change from baseline in weekly ADPS from weeks 1 to 13 was analyzed using a repeated measures ANOVA, a repeated measures mixed effects model (MMRM) based on the restricted maximum likelihood estimation method (REML), with baseline ADPS (< 6 and ≥ 6 points) as covariates and independent variables including treatment group, time point, and interaction between time point and treatment group. The difference between the test and placebo groups was evaluated by calculating the mean difference in the change in ADPS from baseline between groups and its 95% confidence interval (CI).

ADPS response rate, PGIC score, and SF-MPQ (PPI grade)

The ADPS response rate was analyzed by establishing a logistic regression model with whether the response (i.e., ≥ 30% or ≥ 50% decrease in ADPS from baseline) as the dependent variable, and baseline ADPS (<6 and ≥ 6 points), and treatment group as covariates. The difference between the trial group and

the placebo group will be evaluated by calculating the dominance ratio of ADPS response rate (odds ratio) and its 95% CI. PGIC score will be analyzed in 3 cases: PGIC score will be whether much improved or much improved and above (much improved, much improved) or slightly improved and above (much improved, much improved, and slightly improved) respectively as dependent variable and baseline ADPS (< 6 and ≥ 6 points), and treatment group as covariates to establish a logistic regression model for analysis. The difference between the trial group and the placebo group was evaluated by calculating the odds ratio (odds ratio) of the PGIC improvement rate and its 95% CI. SF-MPQ (PPI grade) was analyzed by establishing a logistic regression model with reduction in pain grade from baseline as the dependent variable and baseline ADPS and treatment group as covariates. The difference between the trial group and the placebo group was evaluated by calculating the dominance ratio (odds ratio) of PPI improvement rate and its 95% CI.

VAS scores, ADSIS scores and SF-MPQ pain, EQ-5D-5L

Change from baseline in secondary efficacy indicators (VAS score, ADSIS, SF-MPQ pain rating index , EQ-5D-5L health status score) between the test group and placebo were analyzed using analysis of covariance (ANCOVA), with baseline ADPS (< 6 and ≥ 6 points) included as covariates in the model for calibration analysis and calculation of corresponding between-group mean differences as well as 95% CI.

Sensitivity analysis

Missing data from the efficacy analysis involving the main efficacy index subjects with week 13 ADPS were filled, and different missing data fillings were compared by adding sensitivity analysis. For example, for subjects who dropped out and other subjects with missing ADPS at week 13, the non-randomized missing MI-based method was used as the primary analysis to fill in missing data for week 13 ADPS. Last Observation Carryover (LOCF) was also used to fill the missing week 13 ADPS in the analysis on FAS to compare the sensitivity analysis.

Subgroup Analysis

For subjects who had used acetaminophen during baseline and two weeks before baseline and two weeks before the 13-week visit in the FAS, the primary efficacy end point was compared between the dose groups vs. the placebo group.

Safety analysis

Safety analyses were based on SS. safety assessment variables included AE, ECG, laboratory test values, and vital signs. In SS, safety data were summarized by each treatment group and tabulated for all subjects.

Laboratory test values

The aggregated clinical laboratory data included: routine blood, blood biochemistry, HbA1c, urine routine, coagulation function, and pregnancy tests. For each laboratory test (blood routine, blood biochemistry, HbA1c, urine routine) parameter, the clinical laboratory values recorded at each time point and the change from baseline at each visit and EOT visit were summarized. Each parameter was summarized by treatment group. A cross-tab summary was provided to assess the change in each laboratory parameter from baseline to the EOT visit based on the baseline test results and the post-baseline worst test results of the laboratory tests (routine blood, blood biochemistry, routine urine) items. Laboratory results (routine blood, blood biochemistry, urine routine) are also assigned LNH (L: below normal, N: within normal, H: above normal) categories based on the range of normal values set by the local laboratory or central laboratory and presented in the list. A change table (L, N, and H) was used for baseline and post-dosing results to assess changes in each laboratory parameter from baseline to the EOT visit.

Vital Signs

Vital sign parameters include axillary temperature, systolic blood pressure, diastolic blood pressure, respiratory rate, and pulse rate. Results and changes from baseline in vital sign parameters are summarized by planned time point. A list of vital signs is provided based on subject number. Assign LNH (L, N, and H) categories to vital sign results according to the range of normal values and present them in the list. Changes in vital sign parameters from baseline to the EOT visit were assessed using a change table (L, N, H) for baseline and post-dosing outcomes. Measurements with more than two measurements at a planned visit time point were averaged. All measurements containing measurements at unscheduled visit time points were presented in a list of inventories.

Interim analysis

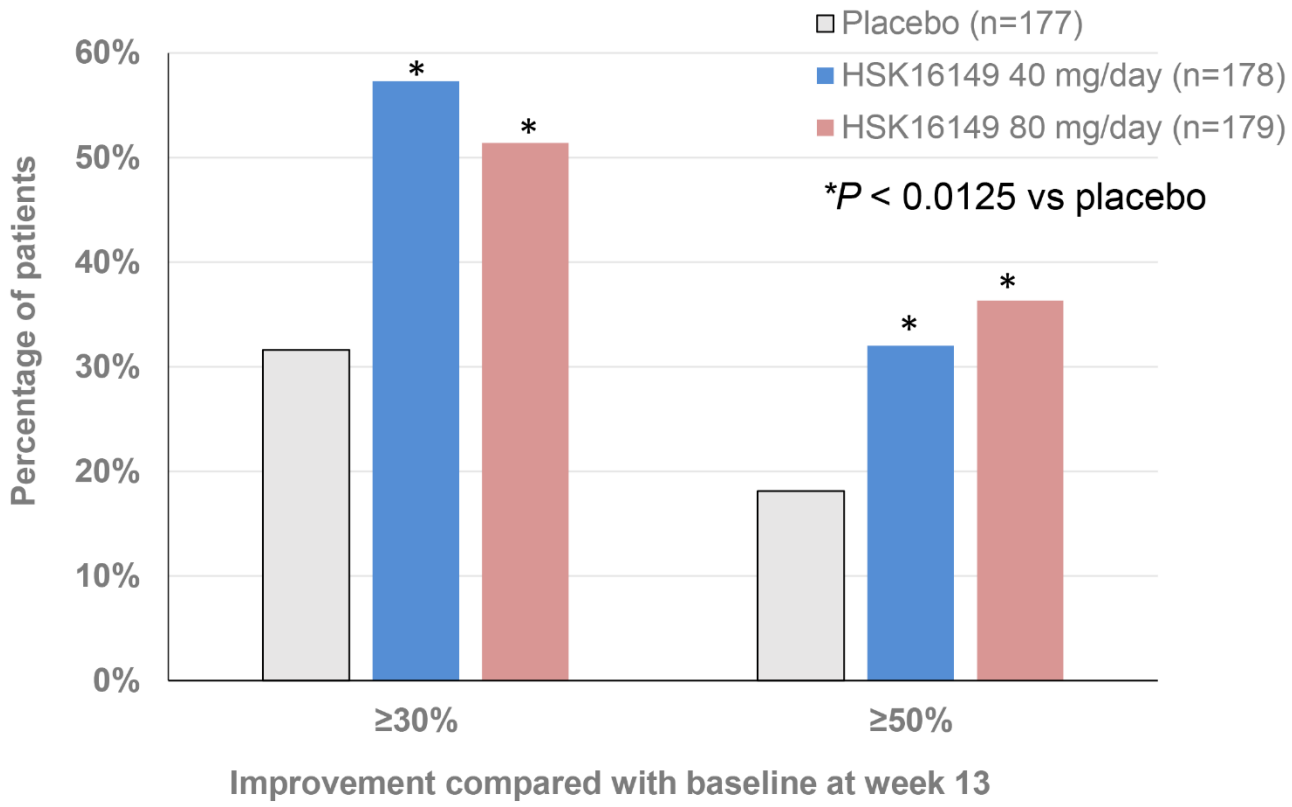
The trial used a seamless phase II/III design, primarily based on the approach used in the article by Friede et al. to select doses for the next phase based on short-term key efficacy indicators; Friede et al. proposed

that in the mid-phase analysis, each trial group was compared with the control group based on short-term key efficacy indicators, and the group with the largest statistic was selected for the confirmatory phase of the study When the final statistical analysis was performed, the selected doses were compared with the control group in each phase based on the primary efficacy index data, and the P-values calculated from the independent data in each phase were combined using a weighted inverse normal method to make statistical inferences.

The primary objective of the interim analysis was to determine the dose to be retained in stage II based on a risk-benefit assessment from the four available validated HSK16149 doses based on stage I data. The primary end point of the interim analysis was the change in ADPS values at week 5 relative to baseline. ADPS data from 360 subjects at week 5 was collected in the interim analysis collect , with approximately 60 subjects in each group. The best dose group was further selected to proceed to the next stage of the clinical trial.

Based on a comprehensive analysis of the results of previous clinical studies of similar drugs, the difference in ADPS change from baseline at 13 weeks of treatment was conservatively estimated to be 0.6, SD was taken as 1.8, one-sided significance level $\alpha=0.025$. The sample size of each group was 143 cases, and considering the 15% drop out rate, the sample size of each group was about 169 cases. The number of treatment dose groups in the second stage was determined based on the results of the mid-term analysis.

eFigure. The Responder Rates



ADPS response rate at week 13 in the full analysis set. The responder rates (≥ 30% and ≥ 50% improvement) were defined as the proportion of patients who had a ≥30% and ≥50% improvement in ADPS vs. baseline. Logistic regression model was established with baseline ADPS (< 6 and ≥ 6) and treatment group as co-variables, and the odds ratio and 95% confidence interval were calculated.

	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo	Pregabalin	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of screening cases							998
Screening failure							228 (22.8)
Failure to meet inclusion criteria or meet exclusion criteria							210 (21.0)
Withdrawal of information							11 (1.1)
Adverse events							0
Other							7 (0.7)
Screening qualified for successful enrollment	179 (17.9)	180 (18.0)	66 (6.6)	64 (6.4)	179 (17.9)	62 (6.2)	770 (77.2)
FAS	178 (99.4)	179 (99.4)	66 (100)	63 (98.4)	177 (98.9)	62 (100)	725 (94.2)
PPS	148 (82.7)	160 (88.9)	52 (78.8)	46 (71.9)	164 (91.6)	54 (87.1)	624 (81.0)
SS	178 (99.4)	180 (100)	66 (100)	64 (100)	176 (98.3)	62 (100)	726 (94.3)
Successful randomization to the group	179 (100)	180 (100)	66 (100)	64 (100)	178 (99.4)	62 (100)	729 (94.7)
Completed study	159 (88.8)	163 (90.6)	53 (80.3)	50 (78.1)	164 (91.6)	55 (88.7)	644 (83.6)
Incomplete study	20 (11.2)	17 (9.4)	13 (19.7)	14 (21.9)	14 (7.8)	7 (11.3)	85 (11.0)
Import failure							41 (5.3)
Main reasons for early discontinuation of subjects from the trial							
Subjects were found to be enrolled in the study in violation of the entry criteria and the investigator determined that the safety of the subjects was compromised	1 (0.6)	0	0	1 (1.6)	0	0	2 (0.3)
Subject withdraws informed consent	4 (2.2)	6 (3.3)	3 (4.5)	0	2 (1.1)	0	15 (2.1)
Insufficient efficacy and, in the investigator's judgment, the need to treat DPNP with other drugs	1 (0.6)	1 (0.6)	0	0	0	1 (1.6)	3 (0.4)
Subject is judged by the investigator to be unsuitable for further study treatment due to the occurrence of AE	7 (3.9)	7 (3.9)	7 (10.6)	10 (15.6)	4 (2.2)	2 (3.2)	37 (5.1)
Research on medication to break blindness	0	0	0	0	1 (0.6)	0	1 (0.1)
Pregnancy	0	0	0	0	0	0	0
Significant noncompliance with protocol-defined procedures including study treatment that, in the judgment of the investigator, affects safety assessment or efficacy analysis	2 (1.1)	0	1 (1.5)	0	1 (0.6)	2 (3.2)	6 (0.8)

missed visits	1 (0.6)	0	0	1 (1.6)	2 (1.1)	0	4 (0.5)
Death	0	0	0	0	0	0	0
Other	4 (2.2)	3 (1.7)	2 (3.0)	2 (3.1)	4 (2.2)	2 (3.2)	17 (2.3)

eTable 1. All Participant Disposition

eTable 2. Summary of Medical History and Present Diagnoses by SOC and PT Classification With a Combined Incidence of ≥ 5.0%

	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo	Pregabalin	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of people with previous and/or current medical history	**176 (98.9)**	**175 (97.8)**	**65 (98.5)**	**61 (96.8)**	**175 (98.9)**	**61 (98.4)**	**713 (98.3)**
All types of neurological disorders	**158 (88.8)**	**148 (82.7)**	**53 (80.3)**	**55 (87.3)**	**158 (89.3)**	**52 (83.9)**	**624 (86.1)**
Diabetic neuropathy	142 (79.8)	133 (74.3)	48 (72.7)	49 (77.8)	146 (82.5)	49 (79.0)	567 (78.2)
Cerebral infarction	20 (11.2)	12 (6.7)	6 (9.1)	7 (11.1)	18 (10.2)	6 (9.7)	69 (9.5)
Carotid atherosclerosis	18 (10.1)	19 (10.6)	1 (1.5)	7 (11.1)	15 (8.5)	5 (8.1)	65 (9.0)
Lacunar cerebral infarction	9 (5.1)	9 (5.0)	3 (4.5)	2 (3.2)	10 (5.6)	4 (6.5)	37 (5.1)
Vascular and Lymphatic Vessel Diseases	**123 (69.1)**	**116 (64.8)**	**40 (60.6)**	**41 (65.1)**	**130 (73.4)**	**39 (62.9)**	**489 (67.4)**
Hypertension	90 (50.6)	83 (46.4)	30 (45.5)	28 (44.4)	92 (52.0)	26 (41.9)	349 (48.1)
Diabetic Vascular Disease	40 (22.5)	36 (20.1)	8 (12.1)	12 (19.0)	45 (25.4)	14 (22.6)	155 (21.4)
Peripheral arterial occlusive disease	12 (6.7)	8 (4.5)	4 (6.1)	3 (4.8)	11 (6.2)	10 (16.1)	48 (6.6)
Atherosclerosis	15 (8.4)	9 (5.0)	3 (4.5)	3 (4.8)	8 (4.5)	1 (1.6)	39 (5.4)
Aortic Atherosclerosis	17 (9.6)	6 (3.4)	1 (1.5)	2 (3.2)	9 (5.1)	1 (1.6)	36 (5.0)
Metabolic and nutritional diseases	**124 (69.7)**	**109 (60.9)**	**49 (74.2)**	**46 (73.0)**	**114 (64.4)**	**40 (64.5)**	**482 (66.5)**
Hyperlipidemia	91 (51.1)	78 (43.6)	32 (48.5)	26 (41.3)	71 (40.1)	23 (37.1)	321 (44.3)
Dyslipidemia	13 (7.3)	17 (9.5)	4 (6.1)	7 (11.1)	20 (11.3)	9 (14.5)	70 (9.7)
Hyperuricemia	19 (10.7)	13 (7.3)	8 (12.1)	6 (9.5)	17 (9.6)	7 (11.3)	70 (9.7)
Hepatobiliary System Diseases	**78 (43.8)**	**65 (36.3)**	**21 (31.8)**	**22 (34.9)**	**69 (39.0)**	**27 (43.5)**	**282 (38.9)**
Hepatic steatosis	55 (30.9)	40 (22.3)	14 (21.2)	14 (22.2)	49 (27.7)	13 (21.0)	185 (25.5)
Gallstone disease	22 (12.4)	20 (11.2)	6 (9.1)	6 (9.5)	16 (9.0)	9 (14.5)	79 (10.9)
Kidney and urinary system diseases	**71 (39.9)**	**59 (33.0)**	**20 (30.3)**	**21 (33.3)**	**59 (33.3)**	**22 (35.5)**	**252 (34.8)**
Diabetic Nephropathy	42 (23.6)	36 (20.1)	11 (16.7)	13 (20.6)	34 (19.2)	14 (22.6)	150 (20.7)
Nephrolithiasis	18 (10.1)	14 (7.8)	4 (6.1)	5 (7.9)	13 (7.3)	7 (11.3)	61 (8.4)
Renal cysts	21 (11.8)	9 (5.0)	5 (7.6)	3 (4.8)	6 (3.4)	5 (8.1)	49 (6.8)
Eye Organ Diseases	**57 (32.0)**	**64 (35.8)**	**16 (24.2)**	**14 (22.2)**	**68 (38.4)**	**21 (33.9)**	**240 (33.1)**
Diabetic retinopathy	46 (25.8)	44 (24.6)	11 (16.7)	10 (15.9)	52 (29.4)	16 (25.8)	179 (24.7)
Cataract	16 (9.0)	18 (10.1)	4 (6.1)	2 (3.2)	19 (10.7)	10 (16.1)	69 (9.5)
Heart Organ Diseases	**71 (39.9)**	**59 (33.0)**	**19 (28.8)**	**13 (20.6)**	**58 (32.8)**	**17 (27.4)**	**237 (32.7)**

Coronary artery sclerosis	40 (22.5)	30 (16.8)	13 (19.7)	6 (9.5)	32 (18.1)	9 (14.5)	130 (17.9)
Myocardial ischemia	10 (5.6)	9 (5.0)	6 (9.1)	3 (4.8)	9 (5.1)	2 (3.2)	39 (5.4)
Infections and Infectious Diseases	**61 (34.3)**	**54 (30.2)**	**24 (36.4)**	**20 (31.7)**	**50 (28.2)**	**20 (32.3)**	**229 (31.6)**
Urinary tract infections	13 (7.3)	16 (8.9)	5 (7.6)	5 (7.9)	15 (8.5)	7 (11.3)	61 (8.4)
Appendicitis	11 (6.2)	8 (4.5)	7 (10.6)	4 (6.3)	12 (6.8)	2 (3.2)	44 (6.1)
Various musculoskeletal and connective tissue diseases	**62 (34.8)**	**44 (24.6)**	**19 (28.8)**	**22 (34.9)**	**51 (28.8)**	**16 (25.8)**	**214 (29.5)**
Intervertebral disc herniation	25 (14.0)	14 (7.8)	8 (12.1)	12 (19.0)	18 (10.2)	7 (11.3)	84 (11.6)
Osteoarthritis of the spine	17 (9.6)	13 (7.3)	5 (7.6)	6 (9.5)	18 (10.2)	5 (8.1)	64 (8.8)
Osteoporosis	14 (7.9)	9 (5.0)	6 (9.1)	5 (7.9)	15 (8.5)	4 (6.5)	53 (7.3)
Various types of examinations	**46 (25.8)**	**43 (24.0)**	**8 (12.1)**	**9 (14.3)**	**52 (29.4)**	**14 (22.6)**	**172 (23.7)**
Respiratory, thoracic and mediastinal diseases	**46 (25.8)**	**42 (23.5)**	**13 (19.7)**	**14 (22.2)**	**37 (20.9)**	**11 (17.7)**	**163 (22.5)**
Lung masses	31 (17.4)	27 (15.1)	8 (12.1)	8 (12.7)	24 (13.6)	9 (14.5)	107 (14.8)
Gastrointestinal system diseases	**46 (25.8)**	**37 (20.7)**	**20 (30.3)**	**7 (11.1)**	**28 (15.8)**	**10 (16.1)**	**148 (20.4)**
Chronic gastritis	21 (11.8)	14 (7.8)	11 (16.7)	6 (9.5)	9 (5.1)	3 (4.8)	64 (8.8)
Reproductive system and breast diseases	**42 (23.6)**	**25 (14.0)**	**8 (12.1)**	**4 (6.3)**	**32 (18.1)**	**12 (19.4)**	**123 (17.0)**
Benign prostatic hyperplasia	20 (11.2)	15 (8.4)	5 (7.6)	2 (3.2)	15 (8.5)	7 (11.3)	64 (8.8)
Endocrine system diseases	**28 (15.7)**	**25 (14.0)**	**11 (16.7)**	**10 (15.9)**	**26 (14.7)**	**11 (17.7)**	**111 (15.3)**
Thyroid masses	20 (11.2)	16 (8.9)	4 (6.1)	7 (11.1)	20 (11.3)	7 (11.3)	74 (10.2)
Benign, malignant and tumors of unknown nature (including cystic and polypoid)	**24 (13.5)**	**13 (7.3)**	**7 (10.6)**	**6 (9.5)**	**30 (16.9)**	**8 (12.9)**	**88 (12.1)**
Uterine smooth muscle tumor	7 (3.9)	5 (2.8)	4 (6.1)	4 (6.3)	16 (9.0)	4 (6.5)	40 (5.5)
All kinds of injuries, poisoning and operational complications	**24 (13.5)**	**13 (7.3)**	**7 (10.6)**	**4 (6.3)**	**19 (10.7)**	**7 (11.3)**	**74 (10.2)**
Diseases of the skin and subcutaneous tissue	**10 (5.6)**	**10 (5.6)**	**5 (7.6)**	**7 (11.1)**	**15 (8.5)**	**2 (3.2)**	**49 (6.8)**
Psychiatric category	**18 (10.1)**	**10 (5.6)**	**6 (9.1)**	**3 (4.8)**	**7 (4.0)**	**5 (8.1)**	**49 (6.8)**

eTable 3. Weekly ADPS Change From Baseline: FAS

		HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo	Pregabalin	Total
Baseline	N	178	179	66	63	177	62	725
	Mean (SD)	5.62 (0.896)	5.64 (0.975)	5.59 (1.030)	5.66 (1.043)	5.61 (0.977)	5.79 (1.030)	5.64 (0.971)
Week 1	N	177	177	63	61	177	62	717
	Mean (SD)	-0.36 (0.706)	-0.35 (0.723)	-0.37 (0.738)	-0.35 (0.798)	-0.11 (0.534)	-0.16 (0.556)	-0.28 (0.679)
Week 2	N	169	168	60	55	173	60	685
	Mean (SD)	-0.70 (1.013)	-0.76 (1.091)	-0.56 (1.012)	-0.80 (1.143)	-0.38 (0.847)	-0.60 (0.806)	-0.62 (0.997)
Week 3	N	170	168	59	54	173	60	684
	Mean (SD)	-0.83 (1.117)	-0.83 (1.210)	-0.68 (1.122)	-1.02 (1.343)	-0.52 (0.998)	-0.72 (0.940)	-0.74 (1.124)
Week 4	N	166	167	59	51	172	59	674
	Mean (SD)	-1.02 (1.103)	-1.09 (1.271)	-0.93 (1.217)	-1.09 (1.115)	-0.67 (1.081)	-0.95 (1.089)	-0.94 (1.159)
Week 5	N	166	167	59	51	171	59	673
	Mean (SD)	-1.12 (1.189)	-1.13 (1.322)	-1.03 (1.278)	-1.13 (1.161)	-0.75 (1.147)	-1.02 (1.119)	-1.01 (1.219)
Week 6	N	164	167	57	51	167	58	664
	Mean (SD)	-1.24 (1.214)	-1.26 (1.384)	-1.20 (1.228)	-1.34 (1.173)	-0.90 (1.231)	-1.28 (1.244)	-1.17 (1.269)
Week 7	N	164	167	57	51	167	58	664
	Mean (SD)	-1.27 (1.310)	-1.34 (1.463)	-1.28 (1.274)	-1.43 (1.308)	-0.94 (1.279)	-1.42 (1.302)	-1.23 (1.346)
Week 8	N	164	164	56	50	167	57	658
	Mean (SD)	-1.42 (1.355)	-1.51 (1.470)	-1.46 (1.306)	-1.52 (1.298)	-0.98 (1.348)	-1.47 (1.301)	-1.35 (1.382)
Week 9	N	163	164	56	50	164	57	654

	Mean (SD)	-1.49 (1.385)	-1.60 (1.509)	-1.51 (1.369)	-1.57 (1.321)	-1.04 (1.394)	-1.52 (1.296)	-1.41 (1.418)
Week 10	N	161	164	55	50	166	56	652
	Mean (SD)	-1.65 (1.411)	-1.69 (1.559)	-1.71 (1.575)	-1.77 (1.440)	-1.08 (1.486)	-1.74 (1.413)	-1.54 (1.504)
Week 11	N	160	163	54	50	166	56	649
	Mean (SD)	-1.70 (1.451)	-1.77 (1.558)	-1.77 (1.623)	-1.81 (1.525)	-1.11 (1.613)	-1.77 (1.427)	-1.59 (1.558)
Week 12	N	158	164	53	50	165	55	645
	Mean (SD)	-2.04 (1.522)	-2.08 (1.703)	-1.95 (1.687)	-2.10 (1.691)	-1.18 (1.648)	-1.97 (1.501)	-1.82 (1.664)
Week 13	N	157	161	53	50	165	54	640
	Mean (SD)	-2.24 (1.550)	-2.16 (1.785)	-2.03 (1.694)	-2.15 (1.790)	-1.23 (1.681)	-2.09 (1.565)	-1.92 (1.721)

ADPS, average daily pain score.

eTable 4. Subgroup Analyses Performed for Participants Who Had Used Acetaminophen During and 2 Weeks Before Baseline and 2 Weeks Before the Week 13 Visit in the FAS

HSK16149	Stage I hypothesis	P value	w1	Stage II hypothesis	P value	w2	Combined P value
40 mg	H_{1234}: $p_{1234,1}$	0.5229	0.5796	H_{1234}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{123}: $p_{123,1}$	0.4641	0.5796	H_{123}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{124}: $p_{124,1}$	0.4641	0.5796	H_{124}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{134}: $p_{134,1}$	0.4641	0.5796	H_{134}: $p_{1,2}$	<.0001	0.8149	<.0001
	H_{12}: $p_{12,1}$	0.3811	0.5796	H_{12}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{13}: $p_{13,1}$	0.3811	0.5796	H_{13}: $p_{1,2}$	<.0001	0.8149	<.0001
	H_{14}: $p_{14,1}$	0.3811	0.5796	H_{14}: $p_{1,2}$	<.0001	0.8149	<.0001
	H_{1}: $p_{1,1}$	0.2511	0.5796	H_{1}: $p_{1,2}$	<.0001	0.8149	<.0001
80 mg	H_{1234}: $p_{1234,1}$	0.5229	0.5796	H_{1234}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{123}: $p_{123,1}$	0.4641	0.5796	H_{123}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{124}: $p_{124,1}$	0.4641	0.5796	H_{124}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{234}: $p_{234,1}$	0.5037	0.5796	H_{234}: $p_{2,2}$	<.0001	0.8149	<.0001
	H_{12}: $p_{12,1}$	0.3811	0.5796	H_{12}: $p_{12,2}$	<.0001	0.8149	<.0001
	H_{23}: $p_{23,1}$	0.418	0.5796	H_{23}: $p_{2,2}$	<.0001	0.8149	<.0001
	H_{24}: $p_{24,1}$	0.418	0.5796	H_{24}: $p_{2,2}$	<.0001	0.8149	<.0001
	H_{2}: $p_{2,1}$	0.2798	0.5796	H_{2}: $p_{2,2}$	<.0001	0.8149	<.0001

Missing Week 13 ADPS were calculated based on multiple fill (MI) for fill. ADPS, average daily pain score.

eTable 5. Week 13 ADPS Score Change From Baseline: FAS by Age

Sub group	Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo
Age < 65	Baseline		(N = 120)	(N = 128)	(N = 45)	(N = 48)	(N = 109)
		N (missing)	120 (0)	128 (0)	45 (0)	48 (0)	109 (0)
		Mean (SD)	5.58 (0.816)	5.78 (1.005)	5.52 (1.051)	5.72 (1.101)	5.56 (0.933)
	Week 13	N (missing)	107 (13)	115 (13)	37 (8)	39 (9)	102 (7)
		Mean (SD)	-2.32 (1.605)	-2.09 (1.758)	-1.80 (1.623)	-2.25 (1.869)	-1.30 (1.734)
		Differences in variation between groups and 95% confidence intervals	-1.0365 (-1.4936, -0.5793)	-0.7463 (-1.1964, -0.2962)			
		P-value for change from baseline at each visit between groups	<.0001	0.0012			
Age > 65	Baseline		(N = 58)	(N = 51)	(N = 21)	(N = 15)	(N = 68)
		N (missing)	58 (0)	51 (0)	21 (0)	15 (0)	68 (0)
		Mean (SD)	5.72 (1.042)	5.28 (0.800)	5.75 (0.991)	5.45 (0.828)	5.69 (1.044)
	Week 13	N (missing)	50 (8)	46 (5)	16 (5)	11 (4)	63 (5)
		Mean (SD)	-2.06 (1.427)	-2.33 (1.859)	-2.55 (1.790)	-1.79 (1.498)	-1.12 (1.599)
		Differences in variation between groups and 95% confidence intervals	-0.8667 (-1.4587, -0.2746)	-1.3601 (-1.9712, -0.7490)			
		P-value for change from baseline at each visit between groups	0.0044	<.0001			

eTable 6. Week 13 ADPS Score Change From Baseline: FAS by DPNP Period

subgroup	Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 150mg	Placebo
DPNP period < 1 year			(N = 92)	(N = 91)	(N = 22)	(N = 35)	(N = 93)
	Baseline	N (missing)	92 (0)	91 (0)	22 (0)	35 (0)	93 (0)
		Mean (SD)	5.62 (0.836)	5.64 (0.985)	5.42 (1.076)	5.51 (1.044)	5.53 (0.958)
	Week 13	N (missing)	83 (9)	82 (9)	18 (4)	27 (8)	88 (5)
		Mean (SD)	-2.38 (1.583)	-1.89 (1.748)	-2.26 (1.926)	-1.92 (1.562)	-1.25 (1.686)
		Differences in variation between groups and 95% confidence intervals	-1.1083 (-1.6024, -0.6141)	-0.6278 (-1.1233, -0.1323)			
		P-value for change from baseline at each visit between groups	<.0001	.013			
DPNP period >1 year	Baseline	N (missing)	86 (0)	88 (0)	44 (0)	28 (0)	84 (0)
		Mean (SD)	5.63 (0.961)	5.64 (0.969)	5.68 (1.008)	5.85 (1.028)	5.69 (0.996)
	Week 13	N (missing)	74 (12)	79 (9)	35 (9)	23 (5)	77 (7)
		Mean (SD)	-2.08 (1.507)	-2.44 (1.790)	-1.91 (1.577)	-2.41 (2.028)	-1.21 (1.686)
		Differences in variation between groups and 95% confidence intervals	-0.8772 (-1.4063, -0.3481)	-1.2334 (-1.7539, -0.7130)			
		P-value for change from baseline at each visit between groups	.0013	<.0001			

eTable 7. Week 13 ADPS Change From Baseline in Sensitivity Analysis: FAS*

HSK16149	Stage I hypothesis	P value	w1	Stage II hypothesis	P value	w2	Combined P value
40 mg	H1234: p1234,1	0.778	0.5838	H1234: p12,2	<.0001	0.8119	<.0001
	H123: p123,1	0.7258	0.5838	H123: p12,2	<.0001	0.8119	<.0001
	H124: p124,1	0.7258	0.5838	H124: p12,2	<.0001	0.8119	<.0001
	H134: p134,1	0.7258	0.5838	H134: p1,2	<.0001	0.8119	<.0001
	H12: p12,1	0.6404	0.5838	H12: p12,2	<.0001	0.8119	<.0001
	H13: p13,1	0.6404	0.5838	H13: p1,2	<.0001	0.8119	<.0001
	H14: p14,1	0.6404	0.5838	H14: p1,2	<.0001	0.8119	<.0001
	H1: p1,1	0.4742	0.5838	H1: p1,2	<.0001	0.8119	<.0001
80 mg	H1234: p1234,1	0.778	0.5838	H1234: p12,2	<.0001	0.8119	<.0001
	H123: p123,1	0.7258	0.5838	H123: p12,2	<.0001	0.8119	<.0001
	H124: p124,1	0.7258	0.5838	H124: p12,2	<.0001	0.8119	<.0001
	H234: p234,1	0.7741	0.5838	H234: p2,2	<.0001	0.8119	<.0001
	H12: p12,1	0.6404	0.5838	H12: p12,2	<.0001	0.8119	<.0001
	H23: p23,1	0.753	0.5838	H23: p2,2	<.0001	0.8119	<.0001
	H24: p24,1	0.6934	0.5838	H24: p2,2	<.0001	0.8119	<.0001
	H2: p2,1	0.6082	0.5838	H2: p2,2	<.0001	0.8119	<.0001

*The missing week 13 ADPS was calculated based on LOCF for filling in the analysis on FAS. ADPS, average daily pain score

eTable 8. Week 13 ADPS Change From Baseline in Sensitivity Analysis: PPS*

HSK16149	Stage I hypothesis	P value	w1	Stage II hypothesis	P value	w2	Combined P value
40 mg	H1234: p1234,1	0.3827	0.5822	H1234: p12,2	<.0001	0.813	<.0001
	H123: p123,1	0.3309	0.5822	H123: p12,2	<.0001	0.813	<.0001
	H124: p124,1	0.3309	0.5822	H124: p12,2	<.0001	0.813	<.0001
	H134: p134,1	0.3309	0.5822	H134: p1,2	<.0001	0.813	<.0001
	H12: p12,1	0.2623	0.5822	H12: p12,2	<.0001	0.813	<.0001
	H13: p13,1	0.2623	0.5822	H13: p1,2	<.0001	0.813	<.0001
	H14: p14,1	0.2623	0.5822	H14: p1,2	<.0001	0.813	<.0001
	H1: p1,1	0.1639	0.5822	H1: p1,2	<.0001	0.813	<.0001
80 mg	H1234: p1234,1	0.3827	0.5822	H1234: p12,2	<.0001	0.813	<.0001
	H123: p123,1	0.3309	0.5822	H123: p12,2	<.0001	0.813	<.0001
	H124: p124,1	0.3309	0.5822	H124: p12,2	<.0001	0.813	<.0001
	H234: p234,1	0.5622	0.5822	H234: p2,2	<.0001	0.813	<.0001
	H12: p12,1	0.2623	0.5822	H12: p12,2	<.0001	0.813	<.0001
	H23: p23,1	0.4737	0.5822	H23: p2,2	<.0001	0.813	<.0001
	H24: p24,1	0.6392	0.5822	H24: p2,2	<.0001	0.813	<.0001
	H2: p2,1	0.5365	0.5822	H2: p2,2	<.0001	0.813	<.0001

*The missing week 13 ADPS was calculated based on MI for filling in the analysis on PPS

eTable 9. Key Secondary Efficacy End Points Weekly ADPS Change From Baseline: FAS

Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo
Baseline	N (missing)	178 (0)	179 (0)	66 (0)	63 (0)	177 (0)
	Mean (SD)	5.62 (0.896)	5.64 (0.975)	5.59 (1.030)	5.66 (1.043)	5.61 (0.977)
Week 1	N (missing)	177 (1)	177 (2)	63 (3)	61 (2)	177 (0)
	Mean (SD)	-0.36 (0.706)	-0.35 (0.723)	-0.37 (0.738)	-0.35 (0.798)	-0.11 (0.534)
	Differences in variation between groups and 95% confidence intervals	-0.2453 (-0.5140, 0.0234)	-0.2332 (-0.5020, 0.0355)			
	P-value for change from baseline at each visit between groups	.074	.089			
Week 2	N (missing)	169 (9)	168 (11)	60 (6)	55 (8)	173 (4)
	Mean (SD)	-0.70 (1.013)	-0.76 (1.091)	-0.56 (1.012)	-0.80 (1.143)	-0.38 (0.847)
	Differences in variation between groups and 95% confidence intervals	-0.3080 (-0.5789, -0.0372)	-0.3631 (-0.6342, -0.0921)			
	P-value for change from baseline at each visit between groups	.026	.0087			
Week 3	N (missing)	170 (8)	168 (11)	59 (7)	54 (9)	173 (4)
	Mean (SD)	-0.83 (1.117)	-0.83 (1.210)	-0.68 (1.122)	-1.02 (1.343)	-0.52 (0.998)
	Differences in variation between groups and 95% confidence intervals	-0.2939 (-0.5646, -0.0231)	-0.2817 (-0.5528, -0.0106)			
	P-value for change from baseline at each visit between groups	.033	.042			
Week 4	N (missing)	166 (12)	167 (12)	59 (7)	51 (12)	172 (5)
	Mean (SD)	-1.02 (1.103)	-1.09 (1.271)	-0.93 (1.217)	-1.09 (1.115)	-0.67 (1.081)
	Differences in variation between groups and 95% confidence intervals	-0.3335 (-0.6050, -0.0620)	-0.3965 (-0.6679, -0.1251)			
	P-value for change from baseline at each visit between groups	.016	.0042			
Week 5	N (missing)	166 (12)	167 (12)	59 (7)	51 (12)	171 (6)
	Mean (SD)	-1.12 (1.189)	-1.13 (1.322)	-1.03 (1.278)	-1.13 (1.161)	-0.75 (1.147)
	Differences in variation between groups and 95% confidence intervals	-0.3601 (-0.6317, -0.0884)	-0.3650 (-0.6365, -0.0934)			
	P-value for change from baseline at each visit between groups	.0094	.0084			

Week 6	N (missing)	164 (14)	167 (12)	57 (9)	51 (12)	167 (10)
	Mean (SD)	-1.24 (1.214)	-1.26 (1.384)	-1.20 (1.228)	-1.34 (1.173)	-0.90 (1.231)
	Differences in variation between groups and 95% confidence intervals	-0.3225 (-0.5950, -0.0500)	-0.3532 (-0.6253, -0.0811)			
	P-value for change from baseline at each visit between groups	.020	.011			
Week 7	N (missing)	164 (14)	167 (12)	57 (9)	51 (12)	167 (10)
	Mean (SD)	-1.27 (1.310)	-1.34 (1.463)	-1.28 (1.274)	-1.43 (1.308)	-0.94 (1.279)
	Differences in variation between groups and 95% confidence intervals	-0.3098 (-0.5823, -0.0374)	-0.3909 (-0.6630, -0.1188)			
	P-value for change from baseline at each visit between groups	.026	.0049			
Week 8	N (missing)	164 (14)	164 (15)	56 (10)	50 (13)	167 (10)
	Mean (SD)	-1.42 (1.355)	-1.51 (1.470)	-1.46 (1.306)	-1.52 (1.298)	-0.98 (1.348)
	Differences in variation between groups and 95% confidence intervals	-0.4049 (-0.6773, -0.1324)	-0.4993 (-0.7718, -0.2268)			
	P-value for change from baseline at each visit between groups	.0036	.0003			
Week 9	N (missing)	163 (15)	164 (15)	56 (10)	50 (13)	164 (13)
	Mean (SD)	-1.49 (1.385)	-1.60 (1.509)	-1.51 (1.369)	-1.57 (1.321)	-1.04 (1.394)
	Differences in variation between groups and 95% confidence intervals	-0.4194 (-0.6924, -0.1464)	-0.5252 (-0.7981, -0.2523)			
	P-value for change from baseline at each visit between groups	.0026	.0002			
Week 10	N (missing)	161 (17)	164 (15)	55 (11)	50 (13)	166 (11)
	Mean (SD)	-1.65 (1.411)	-1.69 (1.559)	-1.71 (1.575)	-1.77 (1.440)	-1.08 (1.486)
	Differences in variation between groups and 95% confidence intervals	-0.5201 (-0.7932, -0.2471)	-0.5648 (-0.8375, -0.2922)			
	P-value for change from baseline at each visit between groups	.0002	<.0001			
Week 11	N (missing)	160 (18)	163 (16)	54 (12)	50 (13)	166 (11)
	Mean (SD)	-1.70 (1.451)	-1.77 (1.558)	-1.77 (1.623)	-1.81 (1.525)	-1.11 (1.613)
	Differences in variation between groups and 95% confidence intervals	-0.5283 (-0.8015, -0.2551)	-0.6305 (-0.9033, -0.3577)			
	P-value for change from baseline at each visit between groups	.0002	<.0001			
Week 12	N (missing)	158 (20)	164 (15)	53 (13)	50 (13)	165 (12)
	Mean (SD)	-2.04 (1.522)	-2.08 (1.703)	-1.95 (1.687)	-2.10 (1.691)	-1.18 (1.648)

	Differences in variation between groups and 95% confidence intervals	-0.7983 (-1.0719, -0.5248)	-0.8630 (-1.1358, -0.5902)			
	P-value for change from baseline at each visit between groups	<.0001	<.0001			
Week 13	N (missing)	157 (21)	161 (18)	53 (13)	50 (13)	165 (12)
	Mean (SD)	-2.24 (1.550)	-2.16 (1.785)	-2.03 (1.694)	-2.15 (1.790)	-1.23 (1.681)
	Differences in variation between groups and 95% confidence intervals	-0.9305 (-1.2042, -0.6567)	-0.8930 (-1.1662, -0.6199)			
	P-value for change from baseline at each visit between groups	<.0001	<.0001			

eTable 10. Week 13 ADSIS Score Change From Baseline: FAS

Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo
Baseline	N (missing)	178 (0)	179 (0)	66 (0)	63 (0)	177 (0)
	Mean (SD)	4.43 (1.697)	4.65 (1.596)	4.90 (1.588)	4.57 (1.618)	4.54 (1.514)
Week 13	N (missing)	157 (21)	161 (18)	53 (13)	50 (13)	165 (12)
	Mean (SD)	-1.73 (1.480)	-1.73 (1.599)	-1.99 (1.889)	-1.61 (1.778)	-0.95 (1.652)
	Differences in variation between groups and 95% confidence intervals	-0.8264 (-1.1512, -0.5017)	-0.7612 (-1.0836, -0.4388)			
	P-value for change from baseline at each visit between groups	<.0001	<.0001			

eTable 11. Week 13 VAS Score Change From Baseline: FAS

Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo
Baseline	N (missing)	178 (0)	179 (0)	66 (0)	63 (0)	177 (0)
	Mean (SD)	57.3 (8.64)	57.7 (9.04)	58.3 (9.86)	57.0 (9.87)	57.3 (9.64)
Fixed dose (W13，D92-1/+2)	N (missing)	157 (21)	161 (18)	53 (13)	50 (13)	164 (13)
	Mean (SD)	-22.9 (16.83)	-23.0 (18.32)	-24.1 (19.01)	-26.1 (18.71)	-14.2 (18.61)
	Differences in variation between groups and 95% confidence intervals	-8.7903 (-12.5915, -4.9891)	-8.7663 (-12.5429, -4.9896)			
	P-value for change from baseline at each visit between groups	<.0001	<.0001			

eTable 12. Week 13 SP-MPQ Score Change From Baseline: FAS

Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo
Baseline	N (missing)	178 (0)	179 (0)	66 (0)	63 (0)	177 (0)
	Mean (SD)	7.70 (5.65)	7.60 (5.64)	9.10 (5.76)	7.30 (4.29)	6.50 (4.00)
Fixed dose(W13，D92-1/+2)	N (missing)	157 (21)	161 (18)	53 (13)	50 (13)	164 (13)
	Mean (SD)	-3.50 (4.41)	-3.10 (4.21)	-4.90 (4.62)	-4.20 (3.97)	-2.0 (4.28)
	Differences in variation between groups and 95% confidence intervals	-1.0748 (-1.8803, -0.2693)	-0.6685 (-1.4691, 0.1321)			
	P-value for change from baseline at each visit between groups	.009	.10			

eTable 13. Week 13 EQ-5D-5L Score Change From Baseline: FAS

Check point	Statistics	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo
Baseline	N (missing)	178 (0)	179 (0)	66 (0)	63 (0)	177 (0)
	Mean(SD)	66.30 (15.31)	65.70 (14.91)	65.80 (15.69)	65.60 (14.68)	66.60 (15.80)
Fixed dose (W13，D92-1/+2)	N (missing)	157 (21)	161 (18)	53 (13)	50 (13)	164 (13)
	Mean(SD)	8.20 (17.27)	6.70 (16.38)	6.90 (19.44)	8.70 (15.39)	3.70 (16.01)
	Differences in variation between groups and 95% confidence intervals	4.1128 (1.0840, 7.1416)	2.7947 (-0.2146, 5.8040)			
	P-value for change from baseline at each visit between groups	.0079	.069			

eTable 14. Week 13 PGIC Score: FAS

	HSK16149 40mg	HSK16149 80mg	Placebo
	(N = 178)	(N = 179)	(N = 177)
PGIC scores greatly improved, n (%)	22 (12.4)	26 (14.5)	15 (8.5)
Response rate Odds ratio (95% CI)	1.6269 (0.8094, 3.2702)	1.9267 (0.9774, 3.7982)	
PGIC score intermediately improved and above, n (%)	80 (44.9)	79 (44.1)	48 (27.1)
Odds ratio (95% CI)	2.5112 (1.5862, 3.9756)	2.3287 (1.4748, 3.6769)	
PGIC score slightly improved and above, n (%)	144 (80.9)	150 (83.8)	116 (65.5)
Response rate Odds ratio (95% CI)	4.6049 (2.3787, 8.9144)	5.6721 (2.8187, 11.4141)	

eTable 15. Week 13 SP-MPQ (PPI): FAS

	HSK16149 40mg	HSK16149 80mg	Placebo
	(N = 178)	(N = 179)	(N = 177)
PPI grade improvement, n (%)	73 (41.0)	63 (35.2)	49 (27.7)
Response Rate, Odds ratio (95% CI)	2.0716 (1.3014, 3.2976)	1.5171 (0.9515, 2.4188)	

* SF-MPQ, the Short Form McGill Pain Questionnaire; PPI, the Present Pain Intensity

eTable 16. Summary of All Adverse Events and Treatment-Emergent Adverse Events

	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo	Pregabalin	Total
	(N =178)	(N =180)	(N =66)	(N =64)	(N =176)	(N =62)	(N =726)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All adverse events (AE)	139 (78.1)	142 (78.9)	50 (75.8)	52 (81.3)	117 (66.5)	45 (72.6)	545 (75.1)
treatment emergent adverse events (TEAE)	136 (76.4)	140 (77.8)	49 (74.2)	51 (79.7)	115 (65.3)	45 (72.6)	536 (73.8)
TEAE Level 3 and above	17 (9.6)	13 (7.2)	3 (4.5)	9 (14.1)	7 (4.0)	2 (3.2)	51 (7.0)
TEAE related to experimental drugs	56 (31.5)	73 (40.6)	32 (48.5)	36 (56.3)	33 (18.8)	21 (33.9)	251 (34.6)
TEAE of level 3 and above related to experimental drugs	3 (1.7)	1 (0.6)	0	1 (1.6)	1 (0.6)	0	6 (0.8)
Serious adverse event (SAE)	11 (6.2)	9 (5.0)	2 (3.0)	10 (15.6)	4 (2.3)	4 (6.5)	40 (5.5)
treatment emergent serious adverse events (TESAE)	11 (6.2)	6 (3.3)	2 (3.0)	9 (14.1)	4 (2.3)	4 (6.5)	36 (5.0)
TESAE associated with experimental drugs	0	1 (0.6)	0	1 (1.6)	0	0	2 (0.3)
TEAE resulting in death	0	0	0	0	0	0	0
TEAE leading to drug suspension	6 (3.4)	4 (2.2)	2 (3.0)	1 (1.6)	3 (1.7)	0	16 (2.2)
TEAE leading to permanent discontinuation	9 (5.1)	9 (5.0)	5 (7.6)	10 (15.6)	5 (2.8)	2 (3.2)	40 (5.5)
TEAE leading to early withdrawal of the subject	6 (3.4)	7 (3.9)	7 (10.6)	9 (14.1)	4 (2.3)	2 (3.2)	35 (4.8)
TEAE related to experimental drug that led to suspension of the subject	2 (1.1)	3 (1.7)	2 (3.0)	1 (1.6)	1 (0.6)	0	9 (1.2)
Trial drug-related TEAEs that resulted in permanent discontinuation of the subject	6 (3.4)	6 (3.3)	5 (7.6)	8 (12.5)	2 (1.1)	1 (1.6)	28 (3.9)
Trial drug-related TEAEs that led to early withdrawal of the subject	3 (1.7)	4 (2.2)	7 (10.6)	8 (12.5)	1 (0.6)	1 (1.6)	24 (3.3)

eTable 17. Summary of Treatment-Period Adverse Events With a Combined Incidence of ≥1.0% by SOC and PT-SS

System Organ Classification Preferred Term	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	Placebo	Pregabalin	Total
	(N =178)	(N =180)	(N =66)	(N =64)	(N =176)	(N =62)	(N =726)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	136 (76.4)	140 (77.8)	49 (74.2)	51 (79.7)	115 (65.3)	45 (72.6)	536 (73.8)
Various types of examinations	58 (32.6)	51 (28.3)	12 (18.2)	14 (21.9)	43 (24.4)	20 (32.3)	198 (27.3)
Weight gain	15 (8.4)	11 (6.1)	4 (6.1)	6 (9.4)	5 (2.8)	7 (11.3)	48 (6.6)
Elevated lipase	7 (3.9)	6 (3.3)	1 (1.5)	0	6 (3.4)	2 (3.2)	22 (3.0)
Elevated blood creatine phosphokinase	7 (3.9)	5 (2.8)	0	1 (1.6)	3 (1.7)	1 (1.6)	17 (2.3)
Presence of urinary ketone bodies	5 (2.8)	3 (1.7)	0	1 (1.6)	6 (3.4)	1 (1.6)	16 (2.2)
Decreased white blood cell count	5 (2.8)	2 (1.1)	0	2 (3.1)	3 (1.7)	2 (3.2)	14 (1.9)
Elevated alanine aminotransferase	0	4 (2.2)	0	2 (3.1)	4 (2.3)	1 (1.6)	11 (1.5)
Decreased platelet count	1 (0.6)	6 (3.3)	0	1 (1.6)	1 (0.6)	2 (3.2)	11 (1.5)
Positive urine leukocytes	3 (1.7)	2 (1.1)	0	1 (1.6)	4 (2.3)	0	10 (1.4)
Urine Protein Detected	1 (0.6)	3 (1.7)	0	1 (1.6)	2 (1.1)	1 (1.6)	8 (1.1)
Elevated blood creatinine	3 (1.7)	0	3 (4.5)	0	1 (0.6)	0	7 (1.0)
Elevated blood uric acid	4 (2.2)	1 (0.6)	0	0	1 (0.6)	1 (1.6)	7 (1.0)
Reduced neutrophil count	2 (1.1)	2 (1.1)	0	0	2 (1.1)	1 (1.6)	7 (1.0)
Metabolic and nutritional disorders	44 (24.7)	38 (21.1)	26 (39.4)	14 (21.9)	32 (18.2)	17 (27.4)	171 (23.6)
Hyperlipidemia	9 (5.1)	13 (7.2)	10 (15.2)	3 (4.7)	13 (7.4)	5 (8.1)	53 (7.3)
Hyperuricemia	16 (9.0)	12 (6.7)	5 (7.6)	5 (7.8)	10 (5.7)	3 (4.8)	51 (7.0)
Hypertriglyceridemia	5 (2.8)	6 (3.3)	4 (6.1)	3 (4.7)	3 (1.7)	2 (3.2)	23 (3.2)
Hypoglycemia	4 (2.2)	1 (0.6)	2 (3.0)	0	2 (1.1)	2 (3.2)	11 (1.5)
Diabetic ketosis	2 (1.1)	1 (0.6)	3 (4.5)	1 (1.6)	3 (1.7)	1 (1.6)	11 (1.5)
Diabetes mellitus	4 (2.2)	0	2 (3.0)	0	2 (1.1)	0	8 (1.1)
All types of neurological disorders	32 (18.0)	56 (31.1)	23 (34.8)	28 (43.8)	15 (8.5)	11 (17.7)	165 (22.7)
Dizziness	24 (13.5)	47 (26.1)	17 (25.8)	19 (29.7)	9 (5.1)	6 (9.7)	122 (16.8)
Drowsiness	7 (3.9)	11 (6.1)	7 (10.6)	9 (14.1)	1 (0.6)	3 (4.8)	38 (5.2)
Headache	2 (1.1)	3 (1.7)	1 (1.5)	1 (1.6)	2 (1.1)	1 (1.6)	10 (1.4)
Diabetic neuropathy	1 (0.6)	0	1 (1.5)	3 (4.7)	1 (0.6)	1 (1.6)	7 (1.0)

Infections and Infectious Diseases	28 (15.7)	27 (15.0)	5 (7.6)	7 (10.9)	28 (15.9)	9 (14.5)	104 (14.3)
Urinary tract infections	9 (5.1)	15 (8.3)	3 (4.5)	5 (7.8)	14 (8.0)	3 (4.8)	49 (6.7)
Upper respiratory tract infections	9 (5.1)	7 (3.9)	1 (1.5)	1 (1.6)	6 (3.4)	5 (8.1)	29 (4.0)
Gastrointestinal system diseases	18 (10.1)	23 (12.8)	7 (10.6)	18 (28.1)	14 (8.0)	4 (6.5)	84 (11.6)
Constipation	4 (2.2)	2 (1.1)	1 (1.5)	3 (4.7)	4 (2.3)	1 (1.6)	15 (2.1)
Diarrhea	5 (2.8)	3 (1.7)	1 (1.5)	1 (1.6)	4 (2.3)	1 (1.6)	15 (2.1)
Nausea	3 (1.7)	5 (2.8)	2 (3.0)	3 (4.7)	1 (0.6)	0	14 (1.9)
Vomiting	0	6 (3.3)	2 (3.0)	4 (6.3)	1 (0.6)	0	13 (1.8)
Systemic diseases and various reactions at the drug administration site	10 (5.6)	16 (8.9)	6 (9.1)	4 (6.3)	8 (4.5)	3 (4.8)	47 (6.5)
Weakness	4 (2.2)	5 (2.8)	2 (3.0)	1 (1.6)	3 (1.7)	1 (1.6)	16 (2.2)
Peripheral edema	2 (1.1)	4 (2.2)	1 (1.5)	2 (3.1)	2 (1.1)	2 (3.2)	13 (1.8)
Kidney and urinary system diseases	10 (5.6)	4 (2.2)	2 (3.0)	3 (4.7)	11 (6.3)	2 (3.2)	32 (4.4)
Diabetic nephropathy	2 (1.1)	1 (0.6)	1 (1.5)	0	3 (1.7)	0	7 (1.0)
Hematuria	2 (1.1)	1 (0.6)	0	0	4 (2.3)	0	7 (1.0)
Cardiac organ disorders	7 (3.9)	9 (5.0)	2 (3.0)	3 (4.7)	7 (4.0)	3 (4.8)	31 (4.3)
Ventricular extra systole	2 (1.1)	2 (1.1)	1 (1.5)	1 (1.6)	2 (1.1)	0	8 (1.1)
Sinus bradycardia	1 (0.6)	1 (0.6)	1 (1.5)	1 (1.6)	2 (1.1)	1 (1.6)	7 (1.0)
Various musculoskeletal and connective tissue disorders	7 (3.9)	3 (1.7)	3 (4.5)	4 (6.3)	5 (2.8)	4 (6.5)	26 (3.6)
Diseases of the hepatobiliary system	6 (3.4)	5 (2.8)	3 (4.5)	5 (7.8)	4 (2.3)	2 (3.2)	25 (3.4)
Abnormal liver function	3 (1.7)	3 (1.7)	2 (3.0)	4 (6.3)	3 (1.7)	2 (3.2)	17 (2.3)
Diseases of the eye organs	7 (3.9)	11 (6.1)	0	0	3 (1.7)	4 (6.5)	25 (3.4)
Blurred vision	2 (1.1)	5 (2.8)	0	0	0	0	7 (1.0)
Psychiatric disorders	4 (2.2)	6 (3.3)	3 (4.5)	2 (3.1)	6 (3.4)	2 (3.2)	23 (3.2)
Insomnia	4 (2.2)	5 (2.8)	2 (3.0)	1 (1.6)	5 (2.8)	2 (3.2)	19 (2.6)
Blood and lymphatic system disorders	4 (2.2)	3 (1.7)	2 (3.0)	4 (6.3)	5 (2.8)	0	18 (2.5)
Anemia	3 (1.7)	3 (1.7)	1 (1.5)	2 (3.1)	5 (2.8)	0	14 (1.9)
Skin and subcutaneous tissue disorders	4 (2.2)	8 (4.4)	2 (3.0)	1 (1.6)	2 (1.1)	0	17 (2.3)
Vascular and Lymphatic Vessel Diseases	7 (3.9)	3 (1.7)	1 (1.5)	1 (1.6)	5 (2.8)	0	17 (2.3)
Hypertension	3 (1.7)	2 (1.1)	0	0	4 (2.3)	0	9 (1.2)
Respiratory, thoracic and mediastinal diseases	1 (0.6)	4 (2.2)	0	5 (7.8)	3 (1.7)	1 (1.6)	14 (1.9)
Injuries, poisoning and operational complications of all kinds	4 (2.2)	4 (2.2)	0	3 (4.7)	2 (1.1)	0	13 (1.8)
Diseases of the ear and vagus	1 (0.6)	1 (0.6)	3 (4.5)	1 (1.6)	1 (0.6)	0	7 (1.0)

eTable 18. Summary of Treatment-Phase Adverse Events With a Combined Incidence of ≥1.0% by SOC and PT and Associated With the Investigational Drug-SS

	HSK16149 40mg	HSK16149 80mg	HSK16149 120mg	HSK16149 160mg	All HSK16149 does groups	Placebo	Pregabalin	Total
	(N =178)	(N =180)	(N =66)	(N =64)	(N =488)	(N =176)	(N =62)	(N =726)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	56 (31.5)	73 (40.6)	32 (48.5)	36 (56.3)	197 (40.4)	33 (18.8)	21 (33.9)	251 (34.6)
All kinds of neurological diseases	24 (13.5)	50 (27.8)	20 (30.3)	24 (37.5)	118 (24.2)	7 (4.0)	8 (12.9)	133 (18.3)
Dizziness	21 (11.8)	42 (23.3)	16 (24.2)	19 (29.7)	98 (20.1)	7 (4.0)	5 (8.1)	110 (15.2)
Drowsiness	6 (3.4)	11 (6.1)	7 (10.6)	8 (12.5)	32 (6.6)	1 (0.6)	3 (4.8)	36 (5.0)
Various types of examinations	17 (9.6)	14 (7.8)	3 (4.5)	9 (14.1)	43 (8.8)	11 (6.3)	7 (11.3)	61 (8.4)
Weight gain	10 (5.6)	5 (2.8)	1 (1.5)	5 (7.8)	21 (4.3)	4 (2.3)	5 (8.1)	30 (4.1)
Elevated lipase	3 (1.7)	2 (1.1)	0	0	5 (1.0)	2 (1.1)	1 (1.6)	8 (1.1)
Metabolic and nutritional disorders	9 (5.1)	5 (2.8)	8 (12.1)	4 (6.3)	26 (5.3)	9 (5.1)	4 (6.5)	39 (5.4)
Hyperuricemia	4 (2.2)	4 (2.2)	2 (3.0)	2 (3.1)	12 (2.5)	4 (2.3)	1 (1.6)	17 (2.3)
Hyperlipidemia	2 (1.1)	0	3 (4.5)	1 (1.6)	6 (1.2)	2 (1.1)	2 (3.2)	10 (1.4)
Hypertriglyceridemia	3 (1.7)	1 (0.6)	2 (3.0)	1 (1.6)	7 (1.4)	1 (0.6)	0	8 (1.1)
Gastrointestinal system disorders	6 (3.4)	11 (6.1)	6 (9.1)	7 (10.9)	30 (6.1)	7 (4.0)	1 (1.6)	38 (5.2)
Nausea	3 (1.7)	4 (2.2)	2 (3.0)	2 (3.1)	11 (2.3)	1 (0.6)	0	12 (1.7)
Vomiting	0	5 (2.8)	2 (3.0)	4 (6.3)	11 (2.3)	1 (0.6)	0	12 (1.7)
Constipation	2 (1.1)	2 (1.1)	1 (1.5)	1 (1.6)	6 (1.2)	3 (1.7)	1 (1.6)	10 (1.4)
Systemic diseases and various reactions at the drug administration site	6 (3.4)	7 (3.9)	4 (6.1)	2 (3.1)	19 (3.9)	3 (1.7)	2 (3.2)	24 (3.3)
Weakness	3 (1.7)	4 (2.2)	2 (3.0)	1 (1.6)	10 (2.0)	2 (1.1)	0	12 (1.7)
Peripheral edema	2 (1.1)	2 (1.1)	1 (1.5)	2 (3.1)	7 (1.4)	1 (0.6)	2 (3.2)	10 (1.4)
Hepatobiliary system disorders	3 (1.7)	1 (0.6)	0	2 (3.1)	6 (1.2)	1 (0.6)	0	7 (1.0)
Abnormal liver function	3 (1.7)	1 (0.6)	0	2 (3.1)	6 (1.2)	1 (0.6)	0	7 (1.0)