Synopsis

Sponsor Janssen Pharmaceutical K.K.	Summary table of each study Relevant place in application dossiers Volume number:	(For official use)
Brand name: Tramcet Combination Tablets		
Active ingredient: Tramadol (JAN) and acetaminophen (JAN)	Page:	

Study Title:
A Phase III Study of JNS013 in Patients with Chronic Pain

Investigators:
A total of 24 investigators including Kenji Miki

Investigator Site:
A total of 24 investigator sites including Amagasaki Chuo Hospital

Published papers:
None

Study Period: May 27, 2008 (Date of informed consent obtained from the first patient) January 5, 2009 (Date of the last observation in the last patient)	Clinical phase: III
	Study type: Confirmatory study

Objectives:
To confirm the analgesic efficacy and safety of JNS013 verses placebo in patients with chronic pain associated with osteoarthritis of the knee or low back pain who could not attain a sufficient pain relief from non-steroidal anti-inflammatory drugs (NSAIDs).

Study methods:
This study was designed as a multicenter, double-blind, randomized withdrawal, placebo-controlled, parallel group comparison study. Patients who were confirmed to be eligible in surveys, observations and examinations conducted in the pretreatment observation period after the first registration, and underwent washout of prohibited medications/prohibited therapies and met the transfer criteria of open-label period were transferred to the open-label period. In the open-label period, one or two tablets of the study medication (JNS013) were given to the patient 4 times daily (not to exceed per day) for 2 weeks. With regard to the dosage in the open-label period, for the first 1 week, one or two tablets were selected by the patient according to the patient's severity of pain and tolerability. For the second 1 week, the dosage for individual patients was fixed, based on efficacy and good tolerability. After the end of the open-label period, patients who met the transfer criteria of double-blind period were registered at secondary registration and transferred to the double-blind period. In the double-blind period, the study drug that was randomly allocated for the double-blind period (JNS013 or placebo) was given to the patient 4 times daily. The dose per administration was to be the same as that for the second 1 week in the open-label period, and treatment was continued for 4 weeks or until the pain relief became insufficient.

Number of patients (planned and analyzed):
Number of patients (planned):
Target number of recruited patients: 260 as the number of patients transferred to open-label period
Number of analyzed patients: 130 as the number of patients transferred to double-blind period (65 per group)

Number of patients (analyzed):
Number of patients who gave informed consent: 321
Number of registered patients at primary registration: 319
Number of patients transferred to double-blind period: 277
Analysis set for safety in open-label period: 277 patients
Analysis set for efficacy in open-label period: 277 patients

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Number of patients transferred to double-blind period (number of patients registered as secondary registration): 187
Safety population (SP): 187 (JNS013 group 94, placebo group 93)
Population analyzed for efficacy
- Full Analysis Set (FAS): 187 (JNS013 group 94, placebo group 93)
- Per Protocol Set (PPS): 180 (JNS013 group 91, placebo group 89)

Number of patients who completed the study: 115 (NS013 group 70, placebo group 45)

Diagnosis and Inclusion Criteria:

1. Patients whose chronic pain due to osteoarthritis of the knee or low back pain is persisting for at least 3 months at the start of pretreatment observation period.
2. Patients whose pain relief was insufficient despite 14-day continuous treatment with an identical oral NSAID at the normal maximum dose during 3 months prior to the pretreatment observation period. For tenoxicam and oxaprozin, the duration of treatment is to be for at least 21 days.
3. Patients whose average pain intensity felt in daily living during 48 hours prior to the start of pretreatment observation period is $\geq$ 40 mm to < 80 mm on the Visual Analog Scale$_{48}$ (VAS$_{48}$).
4. Patients who are 20 years of age or older at the time of informed consent.
5. Gender: Both males and females are acceptable.
6. Therapeutic distinction: Outpatients
7. Patients who can walk without requiring walking aids or someone's assistance.
8. Prior to the conduct of this study, patients who have given their own consent to participation in the study in writing after being given a sufficient explanation about the study medication and this study.

Study medication, Dosage and Treatment Methods :

JNS013 tablets
Content: Tablets containing TRAM 37.5 mg/APAP 325 mg each
Dosage/Treatment Methods: One tablet or two tablets were orally given to patients 4 times daily
(As a one-time dose, one tablet or two tablets were selected by the patient in each administration according to the patient's severity of pain and tolerability during the first 1 week in the open-label period. During the second 1 week in the open-label period and double-blind period, the dosage was fixed for individual patients using a dose with analgesic efficacy and no problem with the tolerability. In the double-blind period, the same dose as that for the second 1 week in the open-label period was used.)

Control Drug, Dosage and Treatment Methods :
Placebo tablets
Content: Placebo tablets indistinguishable from JNS013 in appearance
Dosage/Treatment Methods: In the double-blind period, placebo tablets were orally given to patients at the same dose (number of tablets) as that for the second 1 week in the open-label period.

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Study Period:

The following periods from obtaining consent to the end of follow-up period were considered to be a study period.

(Duration from pretreatment observation period to follow-up period: for 11 weeks)

Pretreatment observation period: for 4 weeks

Open-label period: for 2 weeks

Double-blind period: for 4 weeks (or until treatment was discontinued due to insufficient pain relief)

Follow-up period: for 1 week

Evaluation Criteria:

Efficacy:

Primary endpoint: Duration (number of days) from the start of double-blind period to insufficient pain relief* with the study drug

*If either of the following was met, the pain relief was regarded as insufficient.

1. The value of average pain intensity felt in daily living during the past 24 hours (VAS_{24}) on two consecutive 2 days in double-blind period worsened > 15 mm compared with the average VAS_{24} during 3 days prior to the end of open-lable period.
2. When the patient asked for discontinuation of treatment with the study drug because of insufficient pain relief.

Secondary endpoints:

The mean and mean changes from baseline over time for VAS_{24} score,

PI (Pain Intensity Rating), PID (Pain Intensity Difference; difference between current pain and pain assessment at baseline), and PRID (Pain Relief + PID) were evaluated by patients and averaged for each assessment time. Additionally, TOTPAR (Total Pain Relief), SPID (Sum of Pain Intensity Difference), SPRID (Sum of Pain Relief combined with Pain Intensity Difference): these three efficacy variables were derived from hourly mean pain relief, evaluated by patients and averaged for each assessment day.

Roland-Morris disability questionnaire (RDQ) (only for patients with low back pain), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (only for patients with osteoarthritis of the knee), SF-36v2™ (SF-36)

Safety:

Adverse events, laboratory examinations, blood pressure/pulse rate, body weight

Statistical Methods:

Demographic data and other baseline characteristic data:

In the analysis set for safety in open-label period, FAS and SP, for demographic and other baseline characteristics, descriptive statistics were calculated and the frequency tabulation was conducted. For FAS and SP, the totalization was conducted by treatment group. The same type of totalization was conducted by patient disease (osteoarthritis of the knee, low back pain).

Efficacy:

As a primary analysis of the primary endpoint, for the duration (number of days) to insufficient analgesic efficacy after the start of double-blind period, the superiority of JNS013 to placebo was assessed using the stratified log-rank test with stratification factors of patient disease (osteoarthritis of the knee, low back pain). Patients whose study was discontinued for any reasons other than insufficient pain relief by 4 weeks in double-blind period were cut off at that time, and patients who completed the treatment were handled as cut-off cases at 4 weeks. The percentage of "analgesic efficacy" present was estimated for each treatment group using the Kaplan-Meier method.

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Of secondary endpoints, for VAS_{24}, the mean and mean changes from baseline were calculated by assessment time, and the mean changes from baseline to the final point were compared between the JNS013 group and placebo group using ANCOVA including baseline value as a covariate and patient disease and treatment group as factors. For PID, descriptive statistics were calculated by assessment time, and for PID at the final point, the analysis was conducted in the same manner as that for mean changes from baseline to the final point of VAS_{24}. For PAR and PRID, descriptive statistics were calculated by assessment time point. For SPID, SPRID and TOTPAR, descriptive statistics were calculated by assessment day. For WOMAC and RDQ score, the mean and mean changes from the start of double-blind period were calculated by assessment time point respectively. In SF-36, for each subscale score, descriptive statistics of score and difference from prior to the start of double-blind period were calculated by assessment time point.
For the primary endpoint, subgroup analyses were conducted by patient disease (osteoarthritis of the knee, low back pain), by age, by gender, and by body weight.

Safety:
The number and percentage of patients with adverse events were calculated by period: open-label period, double-blind period and follow-up period. The number and percentage of patients with adverse events/adverse reactions were calculated for the following: the most common AEs with a $\geq$ 5% incidence, adverse events by severity, significant adverse events and adverse reactions, adverse events and adverse reactions by System Organ Class, and adverse events leading to discontinuation of treatment. In the open-label period, the number and percentage of patients with adverse events/adverse reactions were calculated by number of tablets of initial dose; and in the double-blind period, the number and percentage of patients with adverse events/adverse reactions were calculated by patient characteristic (i.e., gender, age, body weight, patient disease, duration from the onset of pain). In laboratory test items, for items of hematological examination and blood chemistry test, descriptive statistics of each test value were calculated by visit. For items of urinalysis, a cross tabulation between prior to study drug treatment in double-blind period and each visit was conducted. For vital signs (i.e., blood pressure, pulse rate, and body weight), descriptive statistics were calculated by testing time.

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Summary—Conclusion

Efficacy results:

The primary analysis set for efficacy assessments was considered to be FAS, and the secondary analysis set was considered to be PPS. The analysis sets for efficacy consisted of 187 patients in FAS (JNS013 group 94 patients, placebo group 93 patients) and 180 patients in PPS (JNS013 group 91 patients, placebo group 89 patients). For the open-label period, 277 patients of the analysis set for efficacy were analyzed.

< Primary endpoint >

In the analysis of the primary endpoint in FAS, the duration from the start of double-blind period to insufficient pain relief was significantly longer in the JNS013 group compared with the placebo group [stratified log-rank test using patient disease (osteoarthritis of the knee, low back pain) as stratification factors; p=0.0001], and the superiority of JNS013 to placebo was confirmed. As a result of a similar stratified log-rank test in PPS, the JNS013 group showed a statistically significant difference compared with the placebo group, similarly to the result in FAS (stratified log-rank test using patient disease as stratification factors; p=0.0001). In the analysis in FAS by patient disease, the JNS013 group also showed a statistically significant difference compared with the placebo group (log-rank test: osteoarthritis of the knee p=0.0008, low back pain p=0.0251).

The proportion of patients with insufficient pain relief after the start of double-blind period was 21.3% (20/94) in the JNS013 group and 46.2% (43/93) in the placebo group. The proportions of patients with insufficient pain relief by patient disease were the following: osteoarthritis of the knee, 15.4% (6/39) in the JNS013 group and 50.0% (18/36) in the placebo group; low back pain, 25.5% (14/55) in the JNS013 group and 43.9% (25/57) in the placebo group. In either disease, the percentage was lower in the JNS013 group compared with the placebo group.

The hazard ratios of JNS013 group to placebo group [two-tailed 95% confidence interval] in all, osteoarthritis and low back pain were 0.377 [0.221;0.641], 0.238 [0.094;0.603] and 0.490 [0.254;0.943], respectively.

Subgroup analyses for the duration to insufficient pain relief after the start of double-blind period were conducted by patient disease (osteoarthritis of the knee and low back pain), by age, by gender, and by body weight. As a result, no marked differences among the subgroups were observed.

< Secondary endpoints >

In addition to the pain intensity (VAS_{24}) used for judgment of the primary endpoint – insufficient pain relief, in secondary endpoints, descriptive statistics were summarized. For PI, PID, PAR, PRID, SPID, TOTPAR, SPRID, RDQ (parameter of ADL), WOMAC and SF-36 (parameter of QOL) as parameters of pain. For VAS_{24}, the mean change (SD) from the baseline to the end in open-label period -28.36 (20.899) mm. In the double-blind period, there was almost no difference of VAS_{24} (average difference -0.67 mm) between baseline of double-blind period and the end in the JNS013 group, and there was an increase in VAS_{24} (average difference 6.21 mm) of that in the placebo group. The difference of VAS_{24} in the JNS013 group showed a statistically significant compared with the placebo group (ANCOVA using baseline of double-blind period for VAS_{24} as a covariate and patient disease and treatment group as factors; p=0.0161).

The mean PI decreased at 1 week from the start of the open-label period. The mean PI was decreased gradually according to 2 hours and 4 hours post-dose at any assessment time In the double-blind period, the mean PI slightly decreased from baseline of double-blind period at 2 to 4 hours after treatment at each assessment time from Week 0 to the end although a slight decreasing trend was observed from Week 0 to the end in both treatment groups.

The mean PID was larger at the start of open-label period compared with Week 1, and increased at 2 to 4 hours after treatment at the start and Week 1. In the mean PID at 4 hours after treatment at the final assessment in double-blind period, no statistically significant difference was observed between the two groups (ANCOVA using the PI at Week 0 in double-blind period as a covariate and patient disease and treatment group as factors; p=0.7388).
The mean PAR and PRID in the open-label period increased in 1 week from the start, and slightly increased at 4 hours after treatment compared with at 2 hours at any assessment time. In the double-blind period, the mean PAR and PRID at 2 hours and at 4 hours after treatment in the JNS013 group changed at a slightly higher level than in the placebo group at each assessment time from Week 0 to the end.
The mean SPID in the open-label period was larger at the start compared with Week 1, and the mean TOTPAR and SPRID in the open-label period increased at Week 1 than at the start. In changes of SPID, TOTPAR and SPRID in the double-blind period, the values in the JNS013 group changed at higher levels than in the placebo group, except similar changes of SPID observed in the JNS013 group and placebo group from Week 2 to the end.
In any assessment item, similar results were observed in FAS and PPS.
All of the RDQ for low back pain, WOMAC for osteoarthritis of the knee, and ADL/QOL parameters of SF-36 related to overall mental aspects showed an improvement from the start to Week 2 in the open-label period. The RDQ and WOMAC in the double-blind period showed an improvement in the JNS013 group, but showed worsening in the placebo group. The difference of SF-36 from the baseline to the end in the double-blind period improved in almost all subscale scores in the JNS013 group, but showed no change or worsening in almost all subscales scores in the placebo group. In the totalization of ADL/QOL parameters, the results were similar to those obtained in FAS and PPS.

Safety results:
< Open-label period >
As adverse events in the open-label period, 610 events occurred in 222 of 277 patients in the analysis set for safety in the open-label period, and the incidence was 80.1%. Of the events, 581 were adverse reactions that occurred in 219 patients, and the incidence was 79.1%.
The most common AEs often observed (≥ 5% incidence) were nausea 45.1% (125/277), somnolence 27.8% (77/277), vomiting 27.4% (76/277), constipation 18.8% (52/277), dizziness 16.2% (45/277), headache 7.6% (21/277), pruritus 6.5% (18/277), and feeling abnormal 5.4% (15/277) relatively. All of the events were adverse reactions except for constipation and dizziness in 1 patient each.
The incidences of adverse events by severity were mild 70.8% (196/277) and moderate 9.4% (26/277), and no severe events occurred. The incidences of adverse reactions by severity were mild 70.0% (194/277) and moderate 9.0% (25/277). moderate adverse events that occurred in at least 2 patients were vomiting 6.5% (18/277), nausea 4.7% (13/277), dizziness 1.1% (3/277), and somnolence and headache 0.7% (2/277) each, and all of them were adverse reactions.
The incidences of adverse events by initial dose in the open-label period were 1 tablet per dose 79.1% (189/239) and 2 tablets per dose 86.8% (33/38). The incidences of adverse reactions by initial dose in the open-label period were 1 tablet per dose 79.1% (189/239) and 2 tablets per dose 86.8% (33/38). The incidence of adverse reactions was 78.7% (188/239) for 1 tablet per dose and 81.6% (31/38) for 2 tablets per dose. The adverse event that occurred most was nausea for1 tablet per dose and 2 tablets per dose, and the incidence was 43.9% (105/239) and 52.6% (20/38), respectively.

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In the incidence of adverse events by patient characteristic, no clear tread was observed.
There was no death or other serious adverse event.
The adverse events and adverse reactions that resulted in discontinuation of the study drug were 83 events in 41 patients and 82 events in 41 patients, respectively, and the incidence was 14.8% for both adverse events and adverse reactions. The adverse events that occurred in at least 2 patients and resulted in discontinuation of the study drug were nausea 8.7% (24/277), vomiting 7.9% (22/277), dizziness 2.5% (7/277), somnolence 1.4% (4/277), and headache, constipation, hyperhidrosis and feeling abnormal 0.7% (2/277) each, and all of them were adverse reactions except dizziness in 1 patient. None of the adverse events that led to discontinuation of the study drug was serious, and they were mild or moderate. All of them recovered without any treatment or by treatment such as drug therapy in 1 to 29 days from the onset, except 1 patient with hypertension. For hypertension, an observation of the patient's course was completed when its relief was confirmed on Day 52 from the onset.
338 significant adverse events occurred in 194 patients, and the incidence was 70.0%. The significant adverse events that occurred in at least 2 patients were nausea 45.1% (125/277), somnolence 27.8% (77/277), vomiting 27.4% (76/277), constipation 18.8% (52/277), and hepatic function abnormal 0.7% (2/277). All of the adverse events were adverse reactions except constipation in 1 patient. All the significant adverse events were events characteristic of opioid analgesics, except for hepatic function abnormal (categorized into adverse events related to liver disorder) and chest discomfort (categorized into adverse events related to adverse events related to cardiac disorders). None of the significant adverse events was serious, and they were mild or moderate. All the events recovered after discontinuation of the study drug in 1-61 days after the onset, without any treatment or by treatment such as drug therapy. There were no clinically significant changes in laboratory test values and vital signs.

< Double-blind period >
With regard to adverse events in the double-blind period, in 187 patients in SP (JNS013 group 94 patients, placebo group 93 patients), 86 events in 47 patients and 75 events in 44 patients occurred in the JNS013 group and in the placebo group, respectively. The incidences were 50.0% and 47.3%, respectively. Of the events, adverse reactions were 66 events in 36 patients and 41 events in 25 patients, respectively. The incidences were 38.3% and 26.9%, respectively.
The adverse events relatively often observed in the JNS013 group were gamma-glutamyltransferase increased 11.7% (11/94), and nasopharyngitis, nausea and blood urea increased 5.3% (5/94) each. The adverse reactions were gamma-glutamyltransferase increased 9.6% (9/94), and nausea and blood urea increased 5.3% (5/94) each. The adverse events relatively often observed in the placebo group were nasopharyngitis 18.3% (17/93) and diarrhoea 5.4% (5/93), and there were no adverse reactions with ≥ 5% incidence.
The incidences of adverse events by severity were mild 47.9% (45/94) and moderate 2.1% (2/94) in the JNS013 group, and mild 47.3% (44/93) and moderate 0% in the placebo group. There were no severe adverse events in either group. The incidences of adverse reactions by severity were mild 37.2% (35/94) and moderate 1.1% (1/94) in the JNS013 group and mild 26.9% (25/93) in the placebo group. The moderate adverse events in the JNS013 group were rectal cancer and hepatic function abnormal 1.1% (1/94) each, and of these, hepatic function abnormal was an adverse reaction.
In the incidences of adverse events by patient characteristic, no clear trend was observed.

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There was no death, and the other serious adverse event was rectal cancer that only occurred in 1 patient in the JNS013 group in the double-blind period. It was unlikely that formation of rectal tumor occurred due to the study medication after 1-month treatment, and therefore, the causal relationship with the study medication was judged as "Not related" by the investigator.
The adverse events that resulted in discontinuation of the study drug were 2.1% (2/94) and 1.1% (1/93) in the JNS013 group and placebo group, respectively, and all of them were adverse reactions. The breakdown of adverse events (adverse reactions) leading to discontinuation of the study drug were insomnia, diarrhoea, nausea and vomiting 1.1% (1/94) each in the JNS013 group; and diarrhoea 1.1% (1/93) in the placebo group. None of the events was serious, and all of them were mild and recovered after discontinuation of the study drug in 2-22 days after the onset, without any treatment or by treatment such as drug therapy.
The incidences of significant adverse events in the JNS013 group and placebo group were 11.7% (11/94) and 8.6% (8/93), respectively. All the events were adverse reactions except 1 patient with constipation in the JNS013 group. The significant adverse events that occurred in ≥ 2 patients were nausea 5.3% (5/94) and constipation 3.2% (3/94) in the JNS013 group, and nausea 3.2% (3/93) and somnolence 2.2% (2/93) in the placebo group. All the significant adverse events were events characteristic of opioid analgesics, except for hepatic function abnormal (categorized into adverse events related to liver disorder) and chest pain (categorized into adverse events related to adverse events related to cardiac disorders). None of the significant adverse events in the JNS013 group was serious, and they were mild or moderate in severity and recovered after discontinuation of the study drug in 2-43 days after the onset, without any treatment or by treatment such as drug therapy, excluding hepatic function abnormal that persisted for 53 days. Hepatic function abnormal was not abated during the observation of the course.
There were no clinically significant changes in laboratory test values and vital signs.

Conclusions:
In patients with chronic pain due to osteoarthritis of the knee or low back pain who could not obtain sufficient pain relief from NSAIDs, 4-8 tablets/day of JNS013 were orally administered for 2 weeks, and as a result, patients who showed the analgesic efficacy were assigned to the placebo or JNS013 treatment. When the study drugs were administered for another 4 weeks under double-blind conditions, the duration to insufficient pain relief was significantly longer in the JNS013 treatment group, and therefore the superiority of JNS013 to placebo was confirmed.
The major adverse events relatively often observed were symptoms characteristic of opioid analgesics, and there was no serious adverse event whose causal relationship with the study medication could not be ruled out. All the adverse events were considered to be manageable within medical care at the outpatient department. There was no significant problem with the safety.
Based on the above, the analgesic efficacy and safety of JNS013 in Japanese patients with chronic pain was confirmed.

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