Synopsis

<table>
<tr><td>Sponsor:
Janssen Pharmaceutical K.K.</td><td rowspan="4">Summary table of each study
Relevant place in application dossiers
Volume number:

Page:</td><td rowspan="4">(For official use)</td></tr>
<tr><td>Brand name:
To be determined.</td></tr>
<tr><td>Active ingredients:
Tramadol hydrochloride (JAN)
Acetaminophen (JAN)</td></tr>
<tr><td colspan="3">Study Title:
A Double-Blind Comparative Study of JNS013 in Patients with Post-Tooth-Extraction Pain</td></tr>
<tr><td colspan="3">Investigator:
A total of 14 investigators including Ken Omura, Professor, Tokyo Medical and Dental University Hospital Faculty of Dentistry</td></tr>
<tr><td colspan="3">Investigator Sites:
A total of 13 medical institutions including Tokyo Medical and Dental University Hospital</td></tr>
<tr><td colspan="3">Published papers:
None</td></tr>
<tr><td colspan="2" rowspan="2">Study Period:
March 25, 2008 (Date of informed consent obtained from first patient)
September 26, 2008 (Date of last observation in last patient)</td><td>Clinical phase:
II/III</td></tr>
<tr><td>Study type:
Confirmatory study</td></tr>
<tr><td colspan="3">Objectives:
The efficacy and safety of JNS013 in single oral dose administration will be assessed in patients with pain associated with extraction of mandibular impacted third molar.
The significance of JNS013 will be confirmed compared with each single dose administration of tramadol hydrochloride (TRAM) alone or acetaminophen (APAP) alone to demonstrate the contribution of each component to the analgesic effect of the combination. In addition, its usefulness in post-tooth-extraction pain will be assessed.</td></tr>
<tr><td colspan="3">Study methods:
This study was planned as a multicenter, double-blind, randomized, active-drug controlled, parallel-group comparison study. Of registered patients after informed consent, those who met the criteria for transfer to the double-blind period were randomized to the JNS013 group (TRAM 75.0 mg / APAP 650 mg), TRAM group (TRAM 75.0 mg) or APAP group (APAP 650 mg) to receive the study drugs (2 tablets and 2 capsules) in single oral dose administration.</td></tr>
<tr><td colspan="3">Number of patients (planned and analyzed):
<< Number of patients (planned)>>
Number of patients transferred to double-blind period: 310 (JNS013 group and APAP group 124 each, TRAM group 62)
Number of patients analyzed: 300 (JNS013 group and APAP group 120 each, TRAM group 60)

<< Number of patients (analyzed) >>
Number of patients who gave informed consent: 396
Number of registered patients: 394
Number of patients transferred to double-blind period: 328
Populations analyzed for efficacy
Full Analysis Set (FAS): 328 patients
Per Protocol Set (PPS): 317 patients
Safety Population (SP): 328 patients</td></tr>
</table>

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Diagnosis and Inclusion Criteria:

<< Inclusion Criteria >>

Patients who met all of the following criteria were enrolled as patients in this study.

(1) Patients planned to receive a tooth extraction of one mandibular impacted third molar.

(2) Patients whose mandibular impacted third molar is in the condition of the mesial inclination, and who are required bone removal and separation of the crown at tooth extraction.

(3) Patients who are at least 20 years of age and younger than 75 years of age at the time of informed consent.

(4) Both males and females are acceptable.

(5) Both outpatients and inpatients are acceptable.

(6) Prior to the conduct of the study, patients who were given a sufficient explanation about the study medication and the study and have given their own consent to participating in the study in writing.

≪Criteria for Transfer to Double-Blind Period ≫

Of registered patients, those who met all of the following criteria were transferred to the double-blind period.

(1) Patients who required bone removal and separation of the crown at tooth extraction.

(2) Patients whose intensity of pain associated with tooth extraction within 2 hours after tooth extraction is ≥ 50.0 mm on the 0 to 100-mm visual analog scale (VAS).

(3) Patients who did not undergo general anesthesia or sedation at tooth extraction.

(4) Patients without an abnormality (including laboratory test values) corresponding to Grade 3 in the "Criteria for severity classification of adverse drug reactions" during the pretreatment observation period.

Study medications, dosage and treatment methods

<< Study medication >>

JNS013: Tablets containing TRAM 37.5 mg/APAP 325 mg each

<< Control drug >>

TRAM: Capsules containing TRAM 37.5 mg each that are indistinguishable from APAP capsules in appearance

APAP: Capsules containing APAP 325 mg each that are indistinguishable from TRAM capsules in appearance

Placebo: Placebo tablets that are indistinguishable from JNS013 tablets , and placebo capsules that are indistinguishable from TRAM and APAP capsules in appearance

<< Dosage and treatment methods >>

At the time of transfer to the double-blind period, the study drugs (2 tablets and 2 capsules) were given to the patients by single oral dose administration. The treatment was given to the patients within 30 minutes after the intensity of pain associated with tooth extraction showed ≥ 50.0 mm on the VAS.

JNS013 group: 2 JNS013 tablets, 2 placebo capsules

TRAM group: 2 TRAM capsules, 2 placebo tablets

APAP group: 2 APAP capsules, 2 placebo tablets

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Study Period:
The following duration from the time of informed consent to the end of follow-up period was considered the study period (for 15 days from the initiation of pretreatment observation period to the end of follow-up period).

Pretreatment observation period: for 7 days
Double-blind period: for 1 day (from investigational treatment to 8 hours after treatment or to rescue analgesic treatment)
Follow-up period: for 7 days

Endpoints:
<< Efficacy >>
Primary endpoint
· Superiority of JNS013 to TRAM and APAP ; Total pain relief over 8 hours (TOTPAR 0-8 hr) ; with respect to the numerical rating scale of 0 (complete relief) to 4 (no relief)

Secondary endpoints:
· Total pain relief (TOTPAR) (0-4 hr, 4-8 hr)
· Sum of pain intensity difference (SPID) (0-8 hr, 0-4 hr, 4-8 hr)
· Sum of pain relief combined with pain intensity difference (SPRID) (0-8 hr, 0-4 hr, 4-8 hr)
· The mean and mean changes over time for VAS_{24} score
· The mean and mean changes over time for Pain intensity difference (PID)
· The mean and mean changes over time for Pain relief rating (PAR)
· The mean and mean changes over time for Pain Relief combined with pain Intensity Difference (PRID)
· Time from investigational treatment to drug response (time to response)
· Time from drug response to recurrence of pain (duration of response)
· Patient's impression
· Proportion of patients treated with rescue analgesics and the time to treatment
· Evaluation according to "Evaluation criteria for efficacy of analgesics in post-tooth-extraction pain"

<< Safety >>
· Adverse events (subjective symptoms, objective findings)
· Laboratory test values
· Blood pressure/pulse rate

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Statistical methods:

<< Demographic data and other baseline characteristics >>

In FAS and SP, descriptive statistics were provided and frequency tabulation was calculated for demographic data and other baseline values by treatment group.

<< Efficacy analyses >>

(1) Primary endpoint

For TOTPAR (0-8 hr), group comparisons were conducted by Fisher's least significant difference (LSD). First of all, testing was conducted by the F test of one-way ANOVA using treatment group as a factor at the two-tailed 5% significance level. As a result, if a significant difference was observed, 2-sample t-test was conducted between the JNS013 group and TRAM group and between the JNS013 group and APAP groups, using the test combined with ANOVA at the two-tailed 5% significance level, respectively. In either comparison, the significance of combination in JNS013 was considered to have been confirmed if the superiority of the drug could be confirmed. Descriptive statistics were calculated by treatment group.

(2) Secondary endpoints

For TOTPAR (0-4 hr, 4-8 hr), SPID (0-8 hr, 0-4 hr, 4-8 hr), SPRID (0-8 hr, 0-4 hr, 4-8 hr), descriptive statistics were calculated, and group comparisons were conducted by Fisher's LSD in the same manner as in the analysis of primary endpoint. For changes of VAS, PID, PAR, PRID, time to response, duration of response, and proportion of patients treated with rescue analgesics and the time to treatment, descriptive statistics were calculated by time point. For patient's impression and evaluation according to "Evaluation criteria for efficacy of analgesics in post-tooth-extraction pain", the frequency tabulation was conducted, and the Wilcoxon rank sum test was conducted between the JNS013 group and TRAM group, and between the JNS013 group and APAP group.

<< Safety analyses >>

For adverse events that occurred after investigational treatment, the incidence was calculated, and the frequency tabulation for the number of patients with events and the number of events was conducted. According to MedDRA/J ver. 11.1, the incidence was calculated by SOC and PT, and the frequency tabulation of the number of patients with events and the number of events was conducted. For blood pressure and pulse rate, descriptive statistics of measured values were calculated by measurement time. For laboratory examinations (hematological examination, blood chemistry test and urinalysis), descriptive statistics of quantitative test values were calculated by measurement time. For the quantitative test of urine, a cross-tabulation between before and after treatment was conducted.

Summary-Conclusion:

<< Efficacy results >>

In the primary population for efficacy assessments -- FAS, the mean ± SD of the primary endpoint, TOTPAR (0-8 hr) was 17.7 ± 7.91 in the JNS013 group, 12.4 ± 8.36 in the TRAM group, and 13.3 ± 8.07 in the APAP group. The JNS013 group showed a higher value compared with the TRAM group and APAP group. Statistically significant differences were observed (Fisher's LSD; $p<0.0001$, respectively), and the analgesic efficacy and significance of combination in JNS013 were confirmed.

Similarly to FAS, the mean TOTPAR (0-8 hr) in PPS was higher in the JNS013 group compared with the TRAM and APAP groups, and statistically significant differences were observed (Fisher's LSD; $p<0.0001$, respectively).

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Summary-Conclusion (continued):
In results of the secondary endpoints in FAS, the mean ± SD of TOTPAR (0-4 hr) was 9.6 ± 3.90 in the JNS013 group, 6.3 ± 4.11 in the TRAM group, and 7.4 ± 3.97 in the APAP group. The JNS013 group showed a higher value compared with the TRAM group and APAP group, and statistically significant differences were observed (Fisher's LSD; $p<0.0001$, respectively). The mean ± SD of TOTPAR (4-8 hr) was 8.0 ± 4.73 in the JNS013 group, 6.1 ± 4.67 in the TRAM group, and 5.9 ± 4.71 in the APAP group. The JNS013 group showed a higher value compared with the TRAM group and APAP group, and statistically significant differences were observed (Fisher's LSD; vs. TRAM group: $p = 0.0033$, vs. APAP group: $p=0.0001$). Similarly to TOTPAR, the mean SPID (0-8 hr, 0-4 hr, 4-8 hr) and the mean SPRID (0-8 hr, 0-4 hr, 4-8 hr) were higher in the JNS013 group compared with the TRAM and APAP groups, and statistically significant differences were observed.

The change (mean) of VAS in the JNS013 group increased most at 2 hours after treatment, and then slowly decreased, but larger than in the TRAM and APAP groups throughout the assessment period.
The changes (mean) over time for PID, PAR and PRID were similar in each treatment group in any endpoint. The JNS013 group showed a highest value at 2 hours or 3 hours after treatment. Then the value slowly decreased, but showed the changes at a higher level compared with the TRAM and APAP groups throughout the assessment period.
In patient's impression, the JNS013 group showed favorable results compared with the TRAM and APAP groups, and statistically significant differences were observed (Wilcoxon rank sum test; vs. TRAM group: $p=0.0002$, vs. APAP group: $p=0.0009$).
The proportion of patients treated with rescue analgesics was lower in the JNS013 group compared with the TRAM and APAP groups. As for the time to the rescue analgesic treatment in the patients treated with rescue analgesics, statistically significant differences were observed in the JNS013 group and APAP group (log-rank test; vs. TRAM group: $p=0.0999$, vs. APAP group: $p=0.0159$).
All results in the secondary endpoints supported the results in the primary endpoint. The results of the secondary endpoints in PPS were similar to those in FAS.

<< Safety results >>
Adverse events were observed in 175 of 328 patients, and the total number of events was 272. The events by treatment group were 144 events in 62.1% (82/132) of the JNS013 group, 62 events in 60.6 % (40/66) of the TRAM group, and 66 events in 40.8% (53/130) of the APAP group.
Adverse reactions were observed in 149 of 328 patients, and the total number of events was 211. The events by treatment group were 116 events in 57.6% (76/132) in the JNS013 group, 52 events in 53.0% (35/66) in the TRAM group, and 43 events in 29.2% (38/130) in the APAP group.
The most common AEs that occurred in the JNS013 group with a $\geq$ 5% incidence were somnolence 29.5% (39/132), nausea 15.2% (20/132), dizziness 9.1% (12/132), blood bilirubin increased 9.1% (12/132), vomiting 7.6% (10/132), and headache 5.3% (7/132). The most common AEs with a $\geq$ 5% incidence in the TRAM group were somnolence 22.7% (15/66), nausea 15.2% (10/66), blood bilirubin increased 9.1% (6/66), dizziness 7.6% (5/66), headache 7.6% (5/66), and feeling abnormal 7.6% (5/66). The most common AEs with a $\geq$ 5% incidence in the APAP group were somnolence 10.8% (14/130), blood bilirubin increased 8.5% (11/130), and alveolar osteitis 7.7% (10/130). Of the adverse events with a high incidence in the JNS013 group, there were some events with a higher incidence in the APAP group, but overall the events were similar to those in the TRAM group. In the incidence in the JNS013 group and TRAM group by event, there was no marked difference between the two groups.

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Summary-Conclusion (continued):

The incidences of adverse events by severity in the JNS013 group were severe 1.5% (2/132), moderate 3.8% (5/132), and mild 56.8% (75/132). In the TRAM group, none of the patients were evaluated to be severe, and the incidences were moderate 1.5% (1/66) and mild 59.1% (39/66). In the APAP group, there was no patients evaluated as severe, and the incidences were moderate 3.1% (4/130) and mild 37.7% (49/130). Most events were mild in any group, but in the JNS013 group, nausea in 2 patients (1.5%) and vomiting in 1 patient (0.8%) were evaluated as severe. These events occurred on the day of study medication, and recovered on that day or the next day without requiring any treatment.

There was no death. The other serious adverse events occurred in 0.8% (1/130; 1 event) of the APAP group. The reported event was “drug hypersensitivity”, and the causal relationship with the study drugs was judged to be “Not related” by the investigator.

The adverse events resulting in discontinuation occurred in 1.5% (1/66; 1 event) of the TRAM group. The reported event was “Post-procedural haemorrhage”, and the causal relationship with the study drugs was judged to be “Not related”.

As adverse events of clinical interest, events characteristic of opioid analgesics occurred in 43.2% (57/132) of the JNS013 group, 34.8% (23/66) of the TRAM group and 14.6% (19/130) of the APAP group, and the incidences in the JNS013 group and TRAM group were high compared with the APAP group. There was no marked difference in the incidence of each event between the JNS013 group and TRAM group. The following adverse events were not observed in any treatment group: constipation, respiratory depression and events suggesting respiratory depression, drug dependence-related events, renal disorder-related events, liver disorder-related events, cardiac disorder-related events and convulsion, and anaphylactic reaction.

In the hematological examination and blood chemistry test, there were no clinically significant changes in the mean difference from baseline. In the urinalysis, there were no clinically significant changes.

In systolic blood pressure, diastolic blood pressure and pulse rate, there were no clinically significant changes in the mean difference from baseline.

<< Conclusion >>

In patients with post-tooth-extraction pain in mandibular impacted third molar, compared with TRAM and APAP, JNS013 showed statistically superior analgesic effects in endpoints for efficacy including the primary endpoint, and therefore the superiority of JNS013 to TRAM and APAP could be observed. Major adverse reactions of JNS013 were symptoms characteristic of opioid analgesics due to TRAM. Overall most events were mild, and the effect of combination on safety was not observed, and there was no significant problem with the tolerability of JNS013.

Based on the above, the significance of combination in JNS013 and the usefulness of the drug for post-tooth-extraction pain were confirmed.

Date of Report:
April 27, 2009

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