2. SYNOPSIS

Name of Sponsor: Janssen Pharmaceutical K. K.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: OneDuro®Patch		
Name of Active Ingredient: Fentanyl (JAN, INN)		

Title of Study: Phase 3 Study of JNS020QD in Patients with Chronic Pain

Investigators:

Masanori Yamauchi and 20 others (See Appendix 16.1.4)

Study Sites:

Department of Anesthesia, Sapporo Medical University Hospital and 18 other sites (See Appendix 16.1.4) (21 departments in total)

Publications: None

Study Period: 28 September 2011 (date of informed consent for the first subject) to 26 March 2013 (last day of observations for the last subject	**Phase of Development:** Phase 3 **Type of study:** Confirmatory study

Objectives:

The primary objectives of this study were to evaluate the efficacy and safety of switching from other opioid analgesics to JNS020QD in subjects with moderate to severe chronic pain controlled by regular doses of these opioid analgesics, and to evaluate the safety and efficacy of long-term (52-week) treatment with JNS020QD after switching.

Methodology:

This was planned as an open-label, uncontrolled, multicenter study.
The study was composed of a screening period (1-2 weeks), Period 1 (a 3-week titration period plus 1-week maintenance period), Period 2 (a 48-week long-term treatment period), a tapering period (if required, 0 to 6 weeks), and a 1-week follow-up period.
The initial dose of JNS020QD was based on the daily dose of opioid analgesic administered on the day before the first treatment with JNS020QD.
In Period 1 (titration period), the dose of JNS020QD could be increased from Treatment Day 3 (Day 3) up to 4 days before the study site visit after 3 weeks (Visit 5), and the appropriate dose for each subject was determined in that period. In the 3-day period before the end of the titration period (the 3-day period before Visit 5), the patch was applied at the dose determined for each subject, without change. In Period 1 (maintenance period), the dose applied on the last day of the titration period (at the clinical examination at Visit 5) was used. Subjects who required a dose increase were withdrawn from the study. In Period 2 (long-term treatment period), the dose of JNS020QD was only increased after consideration by the investigator or subinvestigator of efficacy (VAS score on the day of deciding to increase the dose, the frequency of rescue use on each of the 2 days before the day of deciding to increase the dose, etc.), and the pattern of occurrence of adverse events at each subject visit. Doses were increased in accordance with the specified criteria for increasing the dose in Period 1 (titration period) as a guide. The dose could be increased to a maximum of 20.1 mg. The dose could be increased after previous reductions as appropriate in response to the subject's symptoms or condition, to reach the dose level achieved before dose reduction. A 6-week maximum tapering period from Week 52 after starting treatment with the study agent (or at discontinuation) was permitted.
The JNS020QD patch was applied to a site such as the chest, abdomen, upper arm, or thigh, and replaced daily (approximately every 24 hr) for 52 weeks.

The rescue medications permitted for breakthrough pain were fast-acting oral codeine phosphate or oral morphine hydrochloride.

Number of Subjects (Planned and Analyzed):

Planned:
The target number of subjects for enrollment in this study was 60, comprising at least 8 subjects who were to switch to JNS020QD at a starting dose of 0.84 mg, at least 8 to switch to 1.7 mg, at least 4 to switch to 3.4 mg, and at least 4 to switch to 5 mg. These 60 subjects were to include at least 25 with nociceptive pain and at least 25 with neuropathic pain.

Analyzed:
Number of subjects giving consent: 88
Number of subjects enrolled in Period 1: 77
Number of subjects enrolled in Period 2: 64
Full analysis set (FAS)
- Full analysis set for JNS020QD treatment period (FAS1): 77
- Full analysis set for maintenance period (FAS2): 68

Safety analysis set (SP): 77

Starting dose after switching
- No. of subjects switching to 0.84 mg: 54
- No. of subjects switching to 1.7 mg: 15
- No. of subjects switching to 3.4 mg: 5
- No. of subjects switching to 5 mg: 3

Breakdown by category of pain
- No. of subjects with nociceptive pain: 38
- No. of subjects with neuropathic pain: 39

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria
Patients who met all the following criteria were eligible for entry into the study.

1. Male or female outpatients, aged 20 years or older at the time of informed consent
2. Having pain due to any of the diseases below that has persisted for at least 12 weeks before giving informed consent
   Nociceptive pain
   Osteoarthritis, low back pain
   Neuropathic pain
   Post-herpetic neuralgia, diabetic neuropathic pain, CRPS (complex regional pain syndrome), postoperative pain syndrome
3. Chronic pain described in 2 above that requires treatment with an opioid analgesic
4. Using any of the following opioid analgesics for chronic pain described in 2 above for at least 7 days before giving informed consent, at a constant dose (excluding rescue)
   (1) Oral codeine phosphate (≥120 mg/d)
   (2) Oral morphine hydrochloride (≥20 mg/d and <315 mg/d)
   (3) Transdermal fentanyl (3-day patch, 2.1 mg/3 d, 4.2 mg/3 d, 8.4 mg/3 d, or 12.6 mg/3 d)

(4) Tramadol hydrochloride/acetaminophen tablets (≥4 tablets/d and ≤8 tablets/d)
(5) Transdermal buprenorphine (7-day patch, ≥10 mg/7 d and ≤20 mg/7 d)

5. Using rescue medications no more than twice daily in the 7 days before giving informed consent
6. Mean pain intensity experienced during daily activities throughout 1 day before giving informed consent is no more than 45 mm on the Visual Analogue Scale (VAS)
7. Women must meet any of the following conditions before enrollment in the screening period.
   (1) Postmenopausal. Menopause is defined as follows.
   At least 46 years of age and amenorrheic for at least 18 months
   (2) Menstruating
   – Patients who have been surgically sterilized (infertile because they have undergone hysterectomy or bilateral oophorectomy, tubal ligation, or by other means)
   – If heterosexually active, able to use extremely effective contraceptive methods, including an oral hormonal contraceptive, contraceptive injection, contraceptive patch, intrauterine device, or double barrier method, consistent with the rules of the country or region on contraception for clinic study participants, during participation in the study and for 90 days after receiving the last dose of JNS020QD. Alternatively, patients whose male partners have undergone a sterilization procedure.
   – Not heterosexually active
8. Women of childbearing potential must have a negative hCG β pregnancy test at screening.
9. Men who are sexually active with women of childbearing potential must agree to use a double barrier method of contraception during participation in the study and for 90 days after receiving the last dose of JNS020QD. All men must also agree not to donate sperm during participation in the study and for 90 days after receiving the last dose of JNS020QD.
10. Is personally able to voluntarily comply with the prohibitions and restrictions prescribed in the study protocol.
11. Must understand the objectives of the study and the required procedures of the study, and must have personally and voluntarily given written informed consent to participate in the study.

Criteria for Progression to Period 1 (titration period)

Subjects who met all the criteria listed below for progression to Period 1 (titration period) at the end of the screening period could progress to Period 1 (titration period).

1. In the 7 days before the end of the screening period, received regular treatment for chronic pain with any of the following opioid analgesics at a constant dose (excluding rescue)
   (1) Oral codeine phosphate (≥120 mg/d)
   (2) Oral morphine hydrochloride (≥20 mg/d and <315 mg/d)
   (3) Transdermal fentanyl (3-day patch, 2.1 mg/3 d, 4.2 mg/3 d, 8.4 mg/3 d, or 12.6 mg/3 d)
   (4) Tramadol hydrochloride/acetaminophen tablets (≥4 tablets/d and ≤8 tablets/d)
   (5) Transdermal buprenorphine (7-day patch, ≥10 mg/7 days and ≤20 mg/7 d)
2. Mean VAS score ≤45 mm in the 7 days before the end of the screening period
3. The VAS score on each day in the 7 days before the end of the screening period is within ±15 mm of the mean VAS score in the 7 days before the end of the screening period, calculated in accordance with criterion 2 above
4. Used rescue medication no more than twice a day in the 7 days before the end of the screening period
5. Laboratory values obtained during the screening period that met all the following criteria
   (1) AST (GOT): <2.5 times the upper limit of normal

(2) ALT (GPT): <2.5 times the upper limit of normal
(3) Serum creatinine: <2 times the upper limit of normal

Criteria for Achievement of Individual Dose Adjustment in Period 1 (titration period)

Subjects who met all the criteria for achievement of individual dose adjustment shown below at the end of Period 1 (titration period) could progress to Period 1 (maintenance period).

Criteria for Achievement of Individual Dose Adjustment

Subjects who met all the criteria below were defined as meeting the criteria for achievement of individual dose adjustment.

1. The dose of JNS020QD is constant in the 3 days before the end of the titration period
2. The change from baseline (the mean VAS score in the 7 days before starting treatment with JNS020QD) in the mean VAS score in the 3 days before the end of the titration period is no more than +15 mm
3. Used rescue medication no more than twice a day in the 3 days before the end of the titration period, and the difference from baseline (the mean number of rescue doses in the 7 days before starting treatment with JNS020QD) in the mean number of uses of rescue medication in the 3 days before the end of the titration period is no more than +1.0
4. The dose of JNS020QD during the titration period is no more than the maximum dose prescribed below

Maximum Dose of JNS020QD by Initial Dose

Initial Dose	Maximum Dose
0.84 mg	2.54 mg
1.7 mg	3.4 mg
3.4 mg	7.54 mg
5 mg	10.94 mg

Criteria for Maintenance of Adequate Analgesia in Period 1 (maintenance period)

At the end of Period 1 (maintenance period), the subjects were assessed against the criteria for maintenance of adequate analgesia listed below. Subjects could progress to Period 2 (long-term treatment period) regardless of whether or not the criteria for maintenance of adequate analgesia were met. Before progression to Period 2 (long-term treatment period), subjects were asked to confirm their intention to continue participating in the study in a signed letter of confirmation.

Criteria for Maintenance of Adequate Analgesia

Subjects who met all the criteria below were defined as meeting the criteria for maintenance of adequate analgesia.

1. The dose of JNS020QD is constant in the 7 days before the end of the maintenance period
2. The change from baseline (the mean VAS score in the 7 days before starting treatment with JNS020QD) in the mean VAS score in the 7 days before the end of the maintenance period is no more than +15 mm
3. Used rescue medication no more than twice a day in the 7 days before the end of the maintenance period, and the difference from baseline (the mean number of rescue doses in the 7 days before starting treatment with JNS020QD) in the mean number of uses of rescue medication in the 7 days before the end of the maintenance period is no more than +1.0

Name of Sponsor: Janssen Pharmaceutical K. K.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: OneDuro®Patch		
Name of Active Ingredient: Fentanyl (JAN, INN)		

Study Agent and Batch Number:

JNS020QD supplied for use in this study is a transdermal patch formulation containing fentanyl dissolved in an adhesive polymer base, applied once daily (about every 24 hours). JNS020QD is available in 5 formulations, containing 0.84 mg, 1.7 mg, 3.4 mg, 5 mg, or 6.7 mg of fentanyl.

	JNS020QD				
Amount of fentanyl (mg) in each patch	0.84	1.7	3.4	5.0	6.7
Expiration dates	31 May 2014			31 January 2014	
Lot numbers	BFB3K00	BFB3K00	BFB5E00	BBB7F00	BBB7F00
Batch numbers	0014A				

Dose and Mode of Administration:

Application method:

The JNS020QD patch was applied to a site such as the chest, abdomen, upper arm, or thigh, and replaced daily (approximately every 24 h), for 52 consecutive weeks.

Patch dose:

The starting dose of JNS020QD was based on the daily dose of opioid analgesic administered on the day before the first application of JNS020QD.

In Period 1 (titration period), the dose of JNS020QD could be increased from Treatment Day 3 (Day 3) up to 4 days before the study site visit after 3 weeks (Visit 5), and the appropriate dose for each subject in that particular period was determined. The dose was not changed from the level determined for each subject in the 3-day period before the end of the titration period (the 3-day period before Visit 5). In Period 1 (maintenance period), the dose applied on the last day of the titration period (at the clinical examination at Visit 5) was used. Subjects who required a dose increase were withdrawn from the study. In Period 2 (long-term treatment period), the dose of JNS020QD was only increased after consideration by the investigator or subinvestigator of efficacy (VAS score on the day of deciding to increase the dose, the frequency of rescue use on each of the 2 days before the day of deciding to increase the dose, etc.), and the pattern of occurrence of adverse events at each subject visit. Doses were increased in accordance with the specified criteria for increasing the dose in Period 1 (titration period) as a guide. The dose could be increased to a maximum of 20.1 mg. The dose could be increased after previous reductions as appropriate in response to the subject's symptoms or condition, to reach the dose level achieved before dose reduction. A 6-week maximum tapering period from Week 52 after starting treatment with the study agent (or at discontinuation) was permitted.

Study Period:

Screening period: 1 to 2 weeks

Period 1 (titration period plus maintenance period): 4 weeks

Period 2 (long-term treatment period): 48 weeks

Tapering period (if necessary): 0 to 6 weeks

Follow-up period: 1 week

Endpoints:

Efficacy:

1. Primary endpoint

The adequate analgesia maintenance rate (the proportion of patients who met the criteria for maintenance of adequate analgesia below)*
*The denominator for calculating the adequate analgesia maintenance rate was the number of subjects who met the criteria for achievement of individual dose adjustment.

Criteria for Maintenance of Adequate Analgesia
Subjects who met all the criteria below were defined as meeting the criteria for maintenance of adequate analgesia.

- The dose of JNS020QD is constant in the 7 days before the end of the maintenance period
- The change from baseline (the mean VAS score in the 7 days before starting treatment with JNS020QD) in the mean VAS score in the 7 days before the end of the maintenance period is no more than +15 mm
- Used rescue medication no more than twice a day in the 7 days before the end of the maintenance period, and the difference from baseline (the mean number of rescue doses in the 7 days before starting treatment with JNS020QD) in the mean number of uses of rescue medication in the 7 days before the end of the maintenance period is no more than +1.0

2. Secondary endpoints

(1) Main secondary endpoints

Rate of achievement of individual dose adjustment (the proportion of subjects who meet the criteria for achievement of individual dose adjustment set out below)*

* The denominator for calculating the rate of achievement of individual dose adjustment was the number of subjects who received at least 1 treatment with JNS020QD.

Criteria for Achievement of Individual Dose Adjustment

Subjects who met all the criteria below were defined as meeting the criteria for achievement of individual dose adjustment.

- The dose of JNS020QD is constant in the 3 days before the end of the titration period
- The change from baseline (the mean VAS score in the 7 days before starting treatment with JNS020QD) in the mean VAS score in the 3 days before the end of the titration period is no more than +15 mm
- Used rescue medication no more than twice a day in the 3 days before the end of the titration period, and the difference from baseline (the mean number of rescue doses in the 7 days before starting treatment with JNS020QD) in the mean number of uses of rescue medication in the 3 days before the end of the titration period is no more than +1.0
- The dose of JNS020QD applied in the titration period is no more than the maximum dose prescribed below

Maximum Dose of JNS020QD by Initial Dose

Initial Dose	Maximum Dose
0.84 mg	2.54 mg
1.7 mg	3.4 mg
3.4 mg	7.54 mg
5 mg	10.94 mg

(2) Other secondary endpoints:

- VAS
- Subject's global evaluation
- Pain intensity by categorical scale

- Total duration of pain each day
- Quality of sleep
- Rescue
- Brief Pain Inventory (short form) (BPI-sf)
- SF-36v2™ (SF-36v2)
- Physician's global evaluation

Safety endpoints:

Adverse events
Laboratory tests (hematology, blood biochemistry, urinalysis)
Vital signs (body temperature, pulse rate [sitting], respiratory rate, blood pressure [sitting])
ECG
Questionnaire on opioid withdrawal symptoms (performed only for subjects for whom withdrawal symptoms developed)
Questionnaire on dependency

Statistical Analysis:

1. Efficacy Analysis

(1) Primary endpoint

For subjects who received treatment with JNS020QD at least once and met the criteria for achievement of individual dose adjustment, point estimates and 95% confidence intervals (95% CI) were calculated for the adequate analgesia maintenance rate.

(2) Secondary endpoints

Point estimates and 95% CIs of the rate of achievement of individual dose adjustment were calculated. Descriptive statistics of VAS scores in the 7-day period before starting treatment with JNS020QD, at each evaluation time in Periods 1 and 2, and changes from the mean VAS score in the 7 days before starting treatment with JNS020QD were calculated. For the subject's global evaluation, pain intensity by categorical scale, total time with pain each day, quality of sleep, BPI-sf, SF-36v2, and physician's global evaluation, descriptive statistics for each evaluation time or proportions and their 95% CIs were calculated for binomial categorical data. For non-binomial categorical data, frequency distributions were prepared for each category. For the BPI-sf (Pain Interference Score, Pain Subscale Score, and Total Score) and for each subscale score of SF-36v2, descriptive statistics of scores and changes from baseline at each evaluation time were calculated. For rescue data, descriptive statistics of the number of uses per day were calculated for the 7-day period before starting treatment with JNS020QD and at each evaluation time after starting treatment with JNS020QD.

2. Safety Analysis

The number and proportion (incidence) of subjects with adverse events, and the number of events were calculated for all new adverse events that occurred after starting treatment with JNS020QD or that worsened after starting treatment with JNS020QD (TESS: Treatment Emergent Signs and Symptoms), tabulated by MedDRA/J System Organ Class (SOC) and Preferred Terms (PT). Descriptive statistics were calculated for quantitative laboratory test values obtained at each evaluation time, and cross-tabulations were prepared for pre and post-baseline values of qualitative variables. Descriptive statistics were calculated for total scores at the end of treatment with JNS020QD (or at discontinuation) for the questionnaire on opioid withdrawal symptoms. Total scores were also categorized and frequency tabulations prepared.

For ECG data, frequencies were tabulated for abnormal findings at each evaluation time. For the questionnaire on dependency, frequencies were tabulated for each question.

Summary—Conclusions:

In subjects with moderate to severe chronic pain controlled with regular doses of other opioid analgesics, evaluation of the efficacy and safety of switching from these opioid analgesics to JNS020QD, and of the efficacy and safety of JNS020QD in long-term treatment for 52 weeks after switching yielded the following results.

Efficacy Results:

Among the 77 subjects who were treated with JNS020QD, the proportion of subjects who met the criteria for achievement of individual dose adjustment in Period 1 (titration period: 3 weeks) (rate of achievement of individual dose adjustment: the main secondary endpoint of the study) (95% CI) was 88.3% (68/77) (81.1; 95.5). Sixty-eight subjects who met the criteria for achievement of individual dose adjustment were enrolled in Period 1 (maintenance period: 1 week), and treatment with JNS020QD at the optimal dose determined for each subject in Period 1 (titration period) yielded an adequate analgesia maintenance rate, the primary endpoint of this study, of 92.6% (63/68) (86.4; 98.9). The lower limit (86.4%) of the 95% CI of this maintenance rate exceeded the level of 77.4% prespecified in the protocol.

The mean (SD) VAS score in Period 1 was 30.1 (11.04) mm in the 7-day period before starting treatment with JNS020QD. After starting treatment with JNS020QD, the VAS score was similar to that in the 7-day period before starting treatment with JNS020QD: 30.7 (13.37) mm in the 3-day period before the end of the titration period and 30.2 (11.39) mm in the 7-day period before the end of the maintenance period. Furthermore, the VAS scores in Periods 1 and 2 ranged between 27.9 and 33.3 mm from Week 1 to Week 52, and no substantial changes were seen from those in the 7-day period before starting treatment with JNS020QD.

The proportion (95% CI) of subjects with subject global evaluations of *Neither Satisfied nor Dissatisfied* or above was 89.6% (69/77) (80.6; 95.4) before starting treatment with JNS020QD. At both Week 1 and Week 2, the proportion was 81.8% (63/77) (71.4; 89.7), and ranged from 86.0% to 94.1% in the period from Week 3 to Week 52, a similar level to that before starting treatment with JNS020QD.

Data on pain intensity by categorical scale showed that before starting treatment with JNS020QD, the percentage of subjects was 0% for no pain, 29.9% (23/77) for mild pain, 70.1% (54/77) for moderate pain, and 0% for severe pain. At Week 4, the rates were 0% for no pain, 36.8% (25/68) for mild pain, 63.2% (43/68) for moderate pain, and 0% for severe pain, at Week 24, the rates were 0% for no pain, 36.2% (21/58) for mild pain, 62.1% (36/58) for moderate pain, and 1.7% (1/58) for severe pain, and at Week 52, the rates were 0% for no pain, 28.3% (13/46) for mild pain, 69.6% (32/46) for moderate pain, and 2.2% (1/46) for severe pain. From before starting treatment with JNS020QD to Week 52, there were no substantial changes in the proportion of subjects with pain intensity in each category.

Data for the total duration of pain each day were as follows. Before starting treatment with JNS020QD, 24.7% (19/77) had pain for <4 h, 31.2% (24/77) had pain for ≥4 h and <8 h, 6.5%

(5/77) had pain for ≥8 h and <12 h, 19.5% (15/77) had pain for ≥12 h, and 18.2% (14/77) had pain all day. At Week 4, the percentages were 35.3% (24/68) for <4 h, 23.5% (16/68) for ≥4 h and <8 h, 8.8% (6/68) for ≥8 h and <12 h, 19.1% (13/68) for ≥12 h, and 13.2% (9/68) all day. At Week 24, the percentages were 25.9% (15/58) for <4 h, 20.7% (12/58) for ≥4 h and <8 h, 17.2% (10/58) for ≥8 h and <12 h, 22.4% (13/58) for ≥12 h, and 13.8% (8/58) all day. At Week 52, the percentages were 26.1% (12/46) for <4 h, 19.6% (9/46) for ≥4 h and <8 h, 13.0% (6/46) for ≥8 h and <12 h, 23.9% (11/46) for ≥12 h, and 17.4% (8/46) all day. The categories with high percentages at Week 52 were <4 h, ≥12 h, ≥4 h and <8 h. At the last evaluation time, the highest proportion was reported for <4 h (27.3%, 21/77).

Before starting treatment with JNS020QD, the responses for quality of sleep were as follows: 27.3% (21/77) Slept Well, 61.0% (47/77) Slept Satisfactorily, 10.4% (8/77) Didn't Sleep Well, and 1.3% (1/77) Didn't Sleep at All. At Week 4, the rates were 32.4% (22/68) Slept Well, 47.1% (32/68) Slept Satisfactorily, 20.6% (14/68) Didn't Sleep Well, and 0% Didn't Sleep at All. At Week 24, the rates were 31.0% (18/58) Slept Well, 44.8% (26/58) Slept Satisfactorily, 22.4% (13/58) Didn't Sleep Well, 1.7% (1/58) Didn't Sleep at All. At Week 52, the rates were 30.4% (14/46) Slept Well, 39.1% (18/46) Slept Satisfactorily, 30.4% (14/46) Didn't Sleep Well, and 0% Didn't Sleep at All. From before starting treatment with JNS020QD up to Week 52, the response with approximately the highest percentage was Slept Satisfactorily.

The mean number of rescue doses in Period 1 was 0.1 to 0.2 doses/d in the 7-day period before starting treatment with JNS020QD, and ranged between 0.2 and 0.4 doses/d from starting treatment with JNS020QD up to Day 29. The mean rescue dose was 2.6 to 4.5 mg/d in the 7-day period before starting treatment with JNS020QD, and ranged from 2.8 to 11.2 mg/d from starting treatment with JNS020QD up to Day 29. The mean number of rescue doses in Periods 1 and 2 ranged from 0.2 to 0.4 doses/d from the start of treatment with JNS020QD up to Week 52. At the last evaluation time, the mean number was 0.7 (1.18) doses/d. The mean rescue dose in Periods 1 and 2 ranged from 3.8 to 6.5 mg/d from the start of treatment up to Week 4, and from 5.9 to 12.5 mg/d from Week 6 to Week 52.

The BPI-sf pain interference score (mean [SD]) was 3.4 (2.29) (n=77) before starting treatment with JNS020QD, and ranged from 2.8 to 3.5 from Week 4 to Week 52. The BPI-sf pain subscale was 3.2 (1.29) (n=77) before starting treatment with JNS020QD, and ranged from 3.1 to 3.4 from Week 4 to Week 52. The BPI-sf total score was 3.4 (1.81) (n=77) before starting treatment with JNS020QD, and ranged from 2.9 to 3.4 from Week 4 to Week 52. No substantial changes were seen in any of these scores from before starting treatment with JNS020QD up to Week 52.

The mean (SD) change from baseline in the physical component summary score of SF-36v2 was 0.1 (11.34; n=77) at Week 4, -0.5 (11.01; n=61) at Week 24, and -1.7 (13.31; n=55) at Week 52. The mean (SD) change from baseline in the mental component summary score was 1.0 (7.28; n=77) at Week 4, -1.3 (8.06; n=61) at Week 24, and -0.5 (8.89; n=55) at Week 52. For each of the scores, there were no major changes from those before starting treatment with JNS020QD.

The percentage of subjects with a physician's global evaluation of Effective was 90% or higher at all evaluation times up to Week 52 after starting treatment with JNS020QD.

The endpoints adequate analgesia maintenance rate, rate of achievement of individual dose

adjustment, VAS score, and subject's global evaluation (categorical analysis) were analyzed for the following subgroups: sex (male, female), age (<65 y, ≥65 y), category of chronic pain (nociceptive pain, neuropathic pain), previous opioid used (oral codeine phosphate, oral morphine hydrochloride, transdermal fentanyl, tramadol hydrochloride/acetaminophen tablets, transdermal buprenorphine), and starting dose after switching (0.84 mg, 1.7 mg, 3.4 mg, 5 mg). For each of these endpoints, the results in each of the following subgroups were not substantially different: sex, age, category of chronic pain, and starting dose after switching. For previous opioid used, the subgroup results were not substantially different for the 4 opioids other than transdermal buprenorphine. There were only 3 subjects in the transdermal buprenorphine subgroup, and while 1 subject achieved the primary endpoint, evaluation of efficacy is not possible with such a small number.

Safety Results
The incidence of adverse events in the 77 subjects in SP up to Week 52 of treatment with JNS020QD was 93.5% (72/77), and the incidence of adverse drug reactions was 79.2% (61/77). The more common adverse events (incidence ≥20%) were constipation (40.3%, 31/77), nausea (36.4%, 28/77), nasopharyngitis (35.1%, 27/77), somnolence (29.9%, 23/77), and dizziness (20.8%, 16/77). The causal relationship between nasopharyngitis and JNS020QD was assessed as Not Related in all subjects, and constipation, nausea, somnolence, and dizziness were assessed as adverse drug reactions in most subjects.
Analyzed by severity, 51.9% (40/77) of adverse events were assessed as mild, 40.3% (31/77) as moderate, and 1.3% (1/77) as severe.

The incidence of adverse events by time of onset (each week) in Period 1 (4 weeks) was highest in Week 1 (35.1%, 27/77), then varied from 19.5% to 23.4% in Weeks 2 to 4. The most common (incidence ≥5%) in Week 1 were the characteristic adverse events of opioid analgesics: nausea (13.0%, 10/77), somnolence (11.7%, 9/77), and constipation (5.2%, 4/77). Up to Week 4 after starting treatment with JNS020QD, there were no events for which the incidence increased appreciably with length of treatment. The incidence of adverse events by time of onset (every 4 weeks) in Periods 1 and 2 was highest in Weeks 1-4 (62.3%, 48/77), and then varied from 25.9% to 50.7% from Week 5 to Week 52. The most common adverse events (incidence ≥5%) in Weeks 1-4 were nausea (23.4%, 18/77), somnolence (18.2%, 14/77), constipation (16.9%, 13/77), nasopharyngitis (9.1%, 7/77), application site pruritus (7.8%, 6/77), dizziness (6.5%, 5/77), vomiting and insomnia(5.2% each, 4/77). Up to Week 52 after starting treatment, there were no events for which the incidence increased with length of treatment.

Subgroup analysis for the following revealed no pronounced differences in the results for each subgroup: sex (male, female), age (<65 y, ≥65 y), category of chronic pain (nociceptive pain, neuropathic pain), previous opioid used (oral codeine phosphate, oral morphine hydrochloride, transdermal fentanyl, tramadol hydrochloride/acetaminophen tablets, transdermal buprenorphine), and by starting dose after switching (0.84 mg, 1.7 mg, 3.4 mg, 5 mg).

There were no deaths. The incidence of serious adverse events was 16.9% (13/77, 16 events). There were 5 events in 4 subjects for which a causal relationship with JNS020QD could not be ruled out: cholangitis acute, malaise, drug withdrawal syndrome, and decreased appetite and weight decreased in the same subject.

For other significant adverse events, the incidence of adverse events leading to dose reduction was

18.2% (14/77), and the events occurring in 2 or more subjects were somnolence (7/77, 9.1%), constipation and nausea (3/77 each, 3.9%), and dizziness and malaise (2/77 each, 2.6%). The incidence of adverse events leading to discontinuation of treatment with JNS020QD was 9.1% (7/77, 9 events), and these 9 events consisted of adjustment disorder, dizziness, somnolence, constipation, cholangitis acute, cholecystitis, intervertebral disc protrusion, application site pruritus, and drug withdrawal syndrome. Otherwise, the following characteristic adverse events of opioid analgesics were observed: constipation (40.3%, 31/77), nausea (36.4%, 28/77), somnolence (29.9%, 23/77), vomiting (16.9%, 13/77), and drug withdrawal syndrome (2.6%, 2/77). Skin abnormalities at the application site consisted of application site pruritus (18.2%, 14/77), application site dermatitis (2.6%, 2/77), and application site erythema (1.3%, 1/77).

No clinically important changes were seen in laboratory values or vital signs (body temperature, respiratory rate, blood pressure, and pulse rate). Abnormal ECG findings that were reported as adverse events consisted of supraventricular extrasystoles and ventricular extrasystoles (1 event each). Both events were assessed as not serious and mild in severity, and the causal relationship with JNS020QD was assessed as Not Related for supraventricular extrasystoles and as Doubtfully Related for ventricular extrasystoles.
Evaluations based on the questionnaire on dependency did not show any evidence of dependency or abuse.

Date of Report: 19 June 2013

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.