SYNOPSIS

Date of report: July 11, 2013

Name of Sponsor/Company	Janssen Korea Ltd.
Investigational Product	Jurnista ER Tab.
Active Ingredient	Hydromorphone HCI

Status: Approved

Date: 12 July 2013

Prepared by: Janssen Korea Ltd.

Protocol number: HYD-KOR-4003

Study title: A prospective, open-label, multicenter, single-arm, interventional study to evaluate the Efficacy and Tolerability of Once-Daily OROS hydromorphone for cancer pain treatment in Korean cancer patients

Byname: START4 study

NCT number: NCT01621100

Clinical trial registry number: CR100659

Coordinating investigator: EunKee Song, MD – Chonbuk National University Hospital
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Study centers: A total of 11 institutions, including Konyang University Hospital, Gyeongsang National University Hospital, Dankook University Hospital, Catholic University of Korea Daejeon St. Mary's Hospital, Soon Chun Hyang University Hospital Cheonan, Eulji University Hospital, Chonbuk National University Hospital, Cheongju St. Mary's Hospital, Chungnam National University Hospital, Chungbuk National University Hospital and Chonnam National University Hwasun Hospital participated in this clinical trial.

Publication (reference): This study has not been published yet.

Study period: From December 11, 2011 to September 10, 2012

Phase of development: Phase 4

Objectives: The primary objective was to determine the efficacy of Hydromorphone HCI ER Tab. in cancer pain control by measuring the rate of change in pain intensity between the first and second evaluations after administering it for 2 weeks. The second objectives were to observe the following variables among subjects who used Hydromorphone HCI ER Tab.

- Change in K-BPI between the first evaluation (Day 1) and the second evaluation (Day 15±2)

- Change in EORTC QLQ-C30: Quality of Life between the first evaluation (Day 1) and the second evaluation (Day 15±2)
- Investigators' global assessment at the second evaluation (Day 15±2)
- Patients' global assessment at the second evaluation (Day 15±2)
- Adverse events
- Proportion of subjects who were withdrawn from the study due to an adverse event

Methodology: This was a 14-week, prospective, open-label, multicenter, single-arm study, consisting of 2 weeks of efficacy evaluation period and 12 weeks of extension phase. Subjects used the study drug, Hydromorphone HCI, as an opioid analgesic for 2 weeks and then could voluntarily participate in the extension phase, during which the cancer pain could be controlled by another potent, long-acting opioid analgesic based on the investigator's judgment (subjects were considered to have been withdrawn from the clinical trial if he/she discontinued Hydromorphone HCI to use another potent, long-acting opioid analgesic during the extension period).

Number of subjects (planned and analyzed sample): The total number of the planned sample was 99 subjects.

Diagnosis and main criteria for inclusion:

Subjects were enrolled in this clinical trial if they met the following inclusion criteria:

- Male or female aged 20 years or older
- Subjects who have not used a potent, long-acting opioid analgesic for cancer pain within the last 60 days
- Subjects with average pain intensity of 4 or more on Numeric Rating Scale (NRS) during the last 24 hours
- Subjects who are capable of following general process of the study based on the investigator's judgment
- Women who are
  - post-menopausal (for at least 1 year)
  - sterile (by hysterectomy, bilateral oophorectomy, tubal ligation or other sterilization operations)
  - abstinent (based on the investigator's judgment)
  - using an effective birth control (such as oral contraception, contraceptive injection, contraceptive patch, intrauterine device, double-barrier methods [including condom, diaphragm, cervical cap or spermicidal foam, cream or gel] or sterility of male partner) and agreed to continue the same method during the study period, among Women of childbearing potential
- Male subjects who practices contraception and agreed to not donate sperms for 1 month after using the study drug
- Subjects who provided a written informed consent

Subjects were excluded from the clinical trial if they met any of the following criteria:

- Current or past history of drug or alcohol abuse within the last 6 months
- Hypersensitivity to Hydromorphone HCI
- Serious digestive diseases, such as dysphagia, vomiting, no bowel movement, intestinal obstruction or severe intestinal stenosis, that could affect the absorption and passage of orally administered drugs enough to interrupt their analgesic activity
- Subjects currently using a monoamine oxidase inhibitor or who discontinued it within the last 2 weeks
  *Monoamine oxidase inhibitors: moclobemide, selegiline, toloxatone, etc.
- Subjects who participated in another clinical trial and received a study drug within the last 4 weeks
- Subjects who were deemed not capable of participating in the study by the investigator, based on the warnings, precautions and contraindications of Hydromorphone HCI
- Subjects who are scheduled to receive a radiotherapy between the first and second evaluation dates

Test drug, dose and mode of administration, batch number:

Dose and mode of administration

The starting dose was 4 mg, the lowest dose of Hydromorphone HCI. Once daily administration at 8AM (±1 hour) was recommended. Subject's average pain intensity was evaluated by telephone inquiries every 2 days from Day 3 to Day 13±2, and dose could be increased if the subject's average pain intensity was NRS 4 or above or if the frequency of rescue analgesic (Hydromorphone HCI IR Tab.) consumption for breakthrough pain was 4 times or more over the last 24 hours. Dose was increased by 4 mg until achieving average pain intensity of mild pain or below (NRS 0, 1, 2, 3) in the past 24 hours.

Batch number

Hydromorphone HCI ER Tab. 4mg: 15195, 15525, 15712
Hydromorphone HCI IR Tab. 2mg: JS272, JS273

Reference therapy, dose and mode of administration, batch number: N/A

Duration of treatment: This clinical trial was composed of 2 weeks of efficacy evaluation period and 12 weeks of extension phase.

Criteria for evaluation:

Efficacy endpoints

The primary efficacy endpoint was %PID (Pain Intensity Difference) between the first evaluation (Day 1) and the second evaluation (Day 15±2). The second efficacy endpoints were:

- Change in K-BPI between the first evaluation (Day 1) and the second evaluation (Day 15±2)
- Change in EORTC QLQ-C30: Quality of Life between the first evaluation (Day 1) and the second evaluation (Day 15±2)

- Investigators' global assessment at the second evaluation (Day 15±2)
- Patients' global assessment at the second evaluation (Day 15±2)

Safety endpoints

- Adverse events
- Proportion of subjects who were withdrawn from the study due to an adverse event

Statistical methods:

Determination of sample size

This was a prospective, open-label, multicenter, single-arm study to determine the efficacy of Hydromorphone HCI from collected data of Korean cancer patients with cancer pain. To estimate the sample size, the proportion of subjects with 50% or more pain intensity difference between before and after the administration was hypothesized as 60%. The number of subjects required for 80% statistical power at one-sided significance level of 2.5% was estimated, and the dropout rate was hypothesized as 15%. The estimated number of subjects required for the study was 99 subjects.

Statistical methods for the primary and secondary endpoints

For the primary endpoint analysis, the proportion of subjects with %PID of 50% or more between the baseline and the second evaluation date was measured.

Changes in the second efficacy endpoints between before and after the administration were measured, and the differences were compared using paired t-test or Fisher's exact test for continuous variables and Chi-square test or McNemar's test for categorical variables. Correlation analyses were performed to determine correlation between the variables, and Generalized Linear Model and ANOVA were used to investigate clinical efficacy of Hydromorphone HCI ER.

Criteria of populations

Two sets of populations, Full analysis set (FAS) population and Per Protocol (PP) population, were used for efficacy evaluation of data obtained from the subjects.
The FAS population included participants who received the study drug at least once, excluding those with major deviation of the inclusion/exclusion criteria.
The PP population included subjects who completed the last evaluation without violating the inclusion/exclusion criteria.
The final evaluations of the primary and secondary efficacy endpoints were performed in the FAS population, and results of the primary and secondary efficacy endpoints were presented in the PP population. Safety population, including all subjects who received the study drug at least once, was used for safety and demographic data.

RESULTS:

STUDY POPULATION:

A total of 107 subjects were enrolled, and 105 subjects who received the study drug at least once were included in the Safety population. FAS population included 102 subjects, excluding 3 subjects who violated the inclusion/exclusion criteria or did not participate in efficacy evaluation once after the

administration. PP population included 70 subjects, excluding 32 subjects who violated the protocol or were withdrawn from the study.

EFFICACY RESULTS:

Among 102 subjects in the FAS population, 50.98% (n=52) achieved 50% or more of %PID, with 95% confidence interval ranging from 41.28% to 60.68%. Among 70 subjects in the PP population, 58.57% (n=41) achieved 50% or more of %PID.

% PID						% PID ≥ 50			
	N	mean	± SD	Min	~ Max	n	%	95% CI	
FAS	102	0.39	± 0.35	-1.00	~1.00	52	50.98	(41.28	~60.68)
PP	70	0.45	± 0.29	-0.50	~1.00	41	58.57	(47.03	~70.11)

PID, Pain intensity difference; CI, Confidence interval

Mean pain score (±SD) measured by NRS was 5.6±1.3 at baseline and 3.4±2.1 at the final evaluation, showing statistically significant difference (reduction, 2.2±2.1; p<0.0001).

Among K-BPI score, pain severity score was reduced from 4.8 ±1.2 to 3.3±1.7, with statistically significant difference (p<0.0001), and Pain interference score was also reduced significantly from 3.7±1.6 to 2.8±1.8 (p<0.0001).

	Baseline			End point			Mean Difference (End point -Baseline)				
	N	Mean	±SD	N	Mean	±SD	Mean	±SD	Difference's 95 % CI[1)]		P-value†
FAS											
Pain Severity Score	102	4.8	±1.2	102	3.3	±1.7	-1.5	±1.7	(-1.85	-1.18)	<0.0001
Pain Interference Score	102	3.7	±1.6	102	2.8	±1.8	-1.0	±1.7	(-1.3	-0.61)	<0.0001
PP											
Pain Severity Score	94	4.8	±1.3	94	3.2	±1.6	-1.6	±1.6	(-1.96	-1.30)	<0.0001
Pain Interference Score	94	3.8	±1.6	94	2.7	±1.7	-1.1	±1.5	(-1.46	-0.83)	<0.0001

1) two-sided 95% confidence interval on the treatment difference (Endpoint -Baseline).

† P-values are obtained by paired t-test

Pain Severity Score: This is calculated by adding the scores for questions 2, 3, 4 and 5 and then dividing by 4.

Pain Interference Score: This is calculated by adding the scores for questions 8a, b, c, d, e, f and g and then dividing by 7.

Among 14 subscales of EORTC QLQ-C30, statistically significant change was observed between at the final evaluation compared to the baseline for 10 subscales (Global health status/QoL, Physical functioning, Emotional functioning, Cognitive functioning, Fatigue, Pain, Dyspnea, Insomnia, Diarrhea) but not for the remaining 4 subscales (Nausea and vomiting, Appetite loss, Constipation, Financial difficulties). In the PP population, however, statistically significant change was observed in 11 subscales excluding 3 subscales (Cognitive functioning, Nausea and vomiting and Constipation).

SAFETY RESULTS:

One hundred and ninety-one cases of adverse events occurred in 76 subjects (72.4%) among overall 105 subjects, while 53 cases of adverse drug reaction occurred in 36 subjects (34.3%). Thirty-seven cases of serious adverse events occurred in 28 subjects (26.7%), and 9 (8.6%) of them died.

	n	(%)	Case
Adverse Event	76	(72.4)	191
Adverse Drug Reaction	36	(34.3)	53
Serious Adverse Event	28	(26.7)	37
Death	9	(8.6)	9

The most common adverse events were nausea (18 cases in 16 subjects, 15.2%), vomiting (15 cases in 13 subjects, 12.4%) and constipation (12 cases in 12 subjects, 11.4%), while the most common adverse drug reactions were constipation (n=12, 11.4%), nausea (n=9, 8.6%) and vomiting (n=8, 7.6%).

9 subjects (8.6%) died, with little or no relation to the study drug.

Thirty-seven cases of serious adverse events were reported by 28 subjects (26.7%). Among them 1 case of headache and 1 case of hypophagia were deemed as possibly related to the study drug. These symptoms were relieved after the study drug was discontinued.

Eighteen subjects discontinued the study drug 31 times due to adverse events.

STUDY LIMITATION: Being a single-arm clinical trial, this study might be limited for the evaluation of improvement in subjects' pain intensity as the effect of Hydromorphine HCI ER Tab.

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