SYNOPSIS

Issue Date: 14 September 2009

Name of Sponsor/Company	Janssen-Cilag
Name of Finished Product	Ionsys®
Name of Active Ingredient(s)	fentanyl iontophoretic transdermal system

Protocol No.: FENHYDPAI4012

Title of Study: Comparison of Ionsys® and routine care with morphine IV PCA in the management of early post-operative mobilisation, ability to mobilise and in time to Fitness For Discharge.

EudraCT Number: 2008-000529-20

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Publication (Reference): None

Study Period: 16 May 2008 - 29 September 2008

Phase of Development: Phase IV

Objectives: The primary objective of this study was to demonstrate the superiority of Ionsys over morphine intravenous (IV) patient controlled analgesia (PCA) with regard to the patient's ability to mobilise during the management of acute moderate to severe post-operative pain in patients who had undergone elective major abdominal (abdominal hysterectomy) or orthopaedic surgery (unilateral primary total hip arthroplasty. The patient's ability to mobilise was assessed by combined analysis of patient responses to the following validated questions at specified time points during their hospital residence: 1. Because of the system/device, I had to be careful when I used my hands or arms (to eat, brush teeth or sit up in bed); 2. The system/device made it difficult for me to adjust my position in bed; 3. The system/device interfered with my ability to get out of bed and walk around (to chair in room, to bathroom, to hallway).

The aim of the primary endpoint was to demonstrate the superiority of Ionsys versus morphine IV PCA treatment in patients' mobilisation characteristics as measured at the point when study drug was discontinued. Additional objectives were to: evaluate pain rating on a scale of 0 to 10 using the Numerical Rating Scale (NRS); compare the safety of Ionsys in this surgical population with the safety of morphine IV PCA, as assessed by adverse events (AEs); compare Ionsys use in this surgical population with morphine IV PCA, as assessed by technical failures of the system/device; compare the impact on nursing care of each system using a validated nurse ease of care (EOC) questionnaire; assess the Patient's Global Assessment (PGA) of the method of pain control at the end of study drug; evaluate differences in time taken for the patient to become Fit For Discharge (FFD) according to common medical and nursing criteria; evaluate the impact of pre-operative medication and intra-operative anaesthetic procedures on the time taken to achieve FFD in both treatment groups; and evaluate differences in the time at which the patient is actually discharged from ward care with both treatment modalities, including reasons for delay between the time taken to be medically FFD and the time of actual discharge.

Methods: This was a multicentre, randomised, open-label, active-controlled, parallel-group, prospective Phase IV study. Patients were screened prospectively within 14 days prior to surgery (study enrolment) or as specified by routine practice for pre-operative visits at each study centre. Informed consent was obtained prior to any study related procedures and patients were educated regarding postoperative pain, pain assessment and goals for pain control, and given the opportunity for dialogue with the treatment

providers. Using the NRS, a verbally administered 11-point scale, the patient was asked to determine the pain rating that they considered would not interfere with required activities, which would identify the patient's realistic pain management goal. Following surgery, patients received the study centre's routine (standard) treatment for analgesia and recovered from general, spinal or epidural anaesthesia in the recovery room. Once alert, patients were reassessed for their eligibility to enter the study. Pain intensity experienced by patients was assessed using the NRS; if the score was >4, the medical staff titrated the patient with IV morphine to a level of comfort (NRS score of ≤4) and repeated the final screening procedure until the patient was eligible to enter into the study (NRS score of ≤4) or >6 hours had elapsed since the patient arrived in the recovery room.

Patients meeting all entry requirements were then randomised to receive either Ionsys or morphine IV PCA. Vital signs and NRS score were then measured and recorded (Baseline Assessments). Then either the Ionsys system was applied or a morphine IV PCA device enabled. This time was recorded as Hour 0. Rescue medication in the form of parenteral morphine sulphate was available from time 0 hours to time 3 hours only. Patients could receive non-opioid analgesics intra-operatively or during the post-operative screening or treatment period as required and as per study centre's routine practice. Patients were observed in the recovery room after treatment initiation and in their hospital room for the remainder of the study. It was planned that Ionsys would be removed at the end of each 24-hour treatment period or after a maximum of 80 doses, whichever came first, and a new Ionsys was placed at a different location on their chest or upper outer arm, unless a switch to oral analgesics was indicated. However, in practice, Ionsys could be removed earlier according to clinical needs. The maximum Ionsys treatment duration was 72 hours (3 Ionsys systems). Patients' active study participation ended when they were considered to have achieved FFD, but they were followed up until discharge. Patients used Ionsys or morphine IV PCA to control their post-operative pain after being titrated to comfort with IV morphine and they discontinued study evaluations when they were considered FFD.

Prior to receiving treatment but after screening, patients received general or regional anaesthesia for their surgical procedure. All medications taken within 48 hours prior to surgery, pre-operative medications, intra-operative medications including anaesthetics and analgesics, and post-operative medications taken by, or administered to the patient prior to Ionsys application or prior to the time the IV PCA device was enabled were recorded on the appropriate case report form (CRF). All post-operative medications (except rescue medication, saline and glucose infusions) taken by or administered to the patient after the initial Ionsys application or after the IV PCA device was enabled, including those for the treatment of AEs, were recorded on the CRF, including the drug name, dose, route, dosing frequency, and date of administration. Rescue medication received by the patient was recorded on a separate CRF page. If there were no medical contraindications, the patient could be given one dose of pethidine (0.3-0.5 mg/kg IV) or tramadol (1 mg/kg IV) within 30 minutes of arrival in the recovery room to control post-operative shivering. Antiemetics could be given on-demand or prophylactically, and were recorded on the appropriate CRF. If it was the study centre's routine practice to give them prophylactically, antiemetics were given prior to initiation of PCA and were not to be mixed into the morphine IV PCA system.

Patients could receive non-opioid analgesics (including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS), ketorolac and COX-2 inhibitors) intra-operatively or during the post-operative screening or treatment period according to clinical judgment and the study centre's routine practice. Patients could be switched to oral opioid analgesics only at any time as per the study centre's routine practice. However, this switch to oral opioid analgesics could not begin while the patient was still wearing Ionsys or receiving morphine IV PCA. Because the use of study drug required special patient care and observation, use of the following medicinal products concomitantly with study treatment was cautioned or restricted: other central nervous system depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquilisers, skeletal muscle relaxants, and sedating antihistamines. Monoamine oxidase inhibitors (MAOIs) were not to be used within 14 days of study start.

Number of Subjects (planned and analyzed): It was planned to include approximately 200 patients (100 per group) who were expected to have acute moderate to severe post-operative pain requiring parenteral opioids for at east 24 hours after an elective major abdominal (abdominal hysterectomy) or orthopaedic surgery (unilateral primary total hip arthroplasty). In all, 108 patients were randomised in the

intention to treat (ITT) population (ie, received at least 1 dose of study treatment and had a post-baseline efficacy measure), which included 58 Ionsys patients and 50 morphine IV PCA patients; 91 patients were included in the per-protocol (PP) population (48 Ionsys patients and 43 morphine IV PCA patients).

Diagnosis and Main Criteria for Inclusion: Male and female patients aged 18 years or older who had American Society of Anesthesiology (ASA) pre-operative physical status I or II; were expected to have acute moderate to severe post-operative pain requiring parenteral opioids via PCA for at least 24 hours after an elective major abdominal (abdominal hysterectomy) or orthopaedic surgery (unilateral primary total hip arthroplasty) expected to remain hospitalised for at least 24 hours post-operatively; were capable of understanding and cooperating with the requirements of the study and operating the Fentanyl ITS (Ionsys) or the IV PCA device; had signed and dated an informed consent document; had been admitted to the recovery room after having general anaesthesia, spinal anaesthetic of <4 hours duration of action or epidural anaesthesia (single administration only) during the protocol-specified elective major abdominal or orthopaedic procedure. Patients with epidural or regional anaesthesia were only included if the provided analgesia was short lasting and was only given for the period of surgery and not for the period in the recovery room. When entering the recovery room, patients with epidural or regional anaesthesia had to still qualify for needing parenteral analgesia according to the local hospital standards; were alert and breathing spontaneously for at least 30 minutes in the recovery room; respiratory rate 10 to 24 breaths per minute; oxygen saturation (SpO2) ≥95% (with or without supplemental oxygen), were able to answer questions and follow commands; had a pain score ≤4 out of 10 on a NRS after titration to comfort with IV morphine. In case of abdominal hysterectomy, this was to be measured 5 minutes after deep breathing and coughing.

Test Product, Dose and Mode of Administration, Batch No.: The study drug was commercially available Ionsys systems (iontophoretic transdermal systems) marked as trial medication, and made available by Janssen-Cilag Ltd. Each Ionsys system contained 10.8 mg fentanyl hydrochloride, which was the equivalent of 9.7 mg fentanyl, and released fentanyl in doses of 40 µg, up to a maximum of 3.2 mg (80 doses). Ionsys consists of a compact electronic control system and two hydrogel reservoirs, one of which contains fentanyl hydrochloride, which can be administered upon request and without an injection needle. The upper product part is of white colour and labelled *Ionsys*. Ionsys is approximately 5 cm by 7.5 cm in size and is individually packaged in a rectangular sealed pouch. Each pouch is packaged in a folding cardboard carton. There is one unit per carton. Each system was tested before it was dispensed to a patient to ensure the system was functional. Ionsys consists of a flexible housing that accommodates the internal electronic circuitry, a battery, the fentanyl-containing hydrogel and an externally-operated on-demand, patient-controlled dosing button for the 170 µA current activation. The drug delivery portion of the system contains two hydrogel reservoirs, each 2.75 cm² in area. The anode hydrogel contains 9.7 mg fentanyl base equivalent. The cathode hydrogel contains no active drug. Morphine ampoules were provided by the study centre. Ionsys batch numbers were: 0800385, 0800385, and 812492.

Duration of Treatment: Each Ionsys system delivered 40 µg fentanyl per on-demand dose up to a maximum of 240 µg (6 doses each of 10 minutes duration) per hour, but not more than a maximum of 80 doses within a 24-hour period. A virtually imperceptible low-intensity electric current is used to repel positively charged fentanyl molecules from the system anode through the skin's stratum corneum into the subcutaneous space, to diffuse into the circulatory system. Each system operated for 24 hours following completion of the first dose or for 80 doses, whichever comes first, and then becomes inoperative. A new system was applied every 24 hours if required unless the patient had used 80 doses in less than 24 hours or if the system was removed, when a new system could be applied earlier. Ionsys was applied to the intact non-irritated, non-irradiated skin on the chest or upper, outer arm. Each system contained fentanyl hydrochloride equivalent to 9.7 mg fentanyl base.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the patient's evaluation of their ability to mobilise. This was assessed through a combined analysis of patient responses to the following three validated questions: 1. Because of the system/device, I had to be careful when I used my hands or arms (to eat, brush teeth or sit up in bed); 2. The system/device made it difficult for me to adjust my position in bed; and 3. The system/device interfered with my ability to get out of bed and walk around (to chair in room, to bathroom

in room/ward, to hallway). The three items were scored on a 6-point Likert scale, ranging from *not at all* (score 0) to *a very great deal* (score 5). Assessments were completed hourly during the first 6 hours. If the patient was still receiving study treatment, further assessments were made at 8, 12, 24, 48 and 72 hours after application of Ionsys or enablement of the IV PCA device. Assessments were also made when the patient was FFD and at the point of study drug discontinuation. An assessment was done at the time the patient stopped study drug. This time point formed the basis of the primary efficacy endpoint analysis.

Secondary endpoint measurements included the following:

- Patient's Pain Rating - Pain intensity experienced by the patient was assessed by means of a verbally-administered 11-point NRS (0, no pain, 10, worst possible pain);
- Nurse EOC Questionnaire - 22-item questionnaire that covers three aspects of care delivery associated with acute care pain management systems, ie time consuming, bothersome and satisfaction. Items are scored on a 6-point Likert scale, ranging from *not at all* to *a very great deal*, although there was the option of responding *not responsible for task* for each item included in the Time-Consuming and Bothersome subscales;
- Fit For Discharge - Patients were assessed for their FFD, according to common medical and nursing criteria. Assessments were hourly during the first 6 hours, and further assessments were made at hours 8 and 12. Starting on the first post operative day, and continuing until the patient was considered FFD, assessments were made at least four times during the day at 4-hourly intervals starting in the morning as soon as practicable after the patient had woken. FFD was assessed by the patient fulfilling the following criteria: 1. Retaining fluids and food, 2. Passing urine without the aid of a catheter, 3. Bowel sounds and/or opening 4. Cardiovascular stability, 5. Respiratory stability, 6. No post-operative wound complications, 7. Pain adequately controlled with oral analgesia only, and 8. Adequately mobile according to locally acceptable standards for mobility for surgery type and pre-operative expectations;
- PGA of Method of Pain Control - Collected at the end of study treatment and consisted of a categorical evaluation (poor, fair, good or excellent) of the method of pain control. The following question was read aloud to the patient: Overall, would you rate this PCA (patient controlled analgesia) method of pain control as being, poor, fair, good, or excellent?;
- Number of Doses of Study Treatment Delivered - The estimated total number of doses of fentanyl delivered by patients in the Ionsys group and the cumulative number of doses in the IV PCA group were collected for each patient at multiple time points;
- Rescue Medication - The total dose of morphine used as rescue medication given between 0-3 hours was recorded on the appropriate CRF for each patient);
- Antiemetic Use - The number of doses, strength and specific amount of antiemetics were recorded);
- Non-Opioid Analgesics - The number of doses, strength and specific amount of non-opioid analgesics used intra-operatively and post-operatively were recorded at baseline, at 24 hours and every 24 hours thereafter.

Safety: The safety population was used to assess safety, comprising blood pressure (BP), heart rate and respiratory rate, AEs, concomitant medications and non-routine events.

Statistical Methods:

Efficacy Analyses: An ITT population, including all randomised patients who used the study treatment at least once and who had at least one efficacy measure after system application or device enablement (0 hours), split by treatment group, was used to assess efficacy. The primary efficacy endpoint of the patient's evaluation of their ability to mobilise was assessed using three validated questions at the point of study drug discontinuation and summarised by treatment group at each time point post-dose, with time of study treatment discontinuation analysed as detailed below. An analysis of covariance (ANCOVA), adjusted for treatment, surgery type, and centre was used to assess mobilising ability difference between treatments and produce 95% confidence intervals (CIs), but if the data were not normal an appropriate non-parametric method was used instead. The null hypothesis was that the adjusted mean ability to mobilise at

time of study treatment discontinuation for Ionsys patients was equal to the adjusted mean mobility for morphine IV PCA patients. The alternative hypothesis was that these were not equal.

Secondary efficacy analyses included:

- Ability to Mobilise - A PP population (defined as a sub-population of the ITT Population, excluding all major protocol violators and patients with no efficacy data after 3 hours) was used for a confirmatory analysis of the primary efficacy endpoint and repeated with study treatment duration as a covariate. The ability to mobilise was assessed using ANCOVA. Mobilisation characteristics at study drug discontinuation were assessed separately for each surgery type and centre by treatment difference and 95% CIs;
- Patient's Pain Rating - Absolute and change from baseline NRS scores were presented by treatment group. An ANCOVA, adjusted for surgery type, centre, treatment, and baseline pain intensity was used to analyse differences in the last mean score at study drug discontinuation. Appropriate transformations or non-parametric methods were used if normality assumptions were not met;
- Time to FFD and Actual Discharge - A log-rank test, stratified for surgery type, assessed time to FFD and Kaplan-Meier plots presented time to actual discharge. A Cox-proportional hazards model assessed the impact of pre-operative medication and intra-operative anaesthetic procedures on time to FFD including patient requirement of a pre-operative medication or intra-operative anaesthetic procedure as a covariate. The interaction between treatment group and pre-operative medication or intra-operative anaesthetic procedure was presented with 95% CIs. Kaplan-Meier plots were presented separately for patients who required pre-operative medication or intra-operative anaesthetic procedures versus patients who had not, split by treatment group. The same methods used to assess time to FFD were used to assess the time to first positive response for each FFD criteria question;
- Nurse EOC Questionnaire - The questionnaire responses were used to calculate domain and total scores, summarised by treatment group and time point. Nurse EOC questionnaire scores were assessed using ANCOVA;
- Rescue Medication Use - The number and percentages of patients who used rescue medication in the first 3 hours post randomisation for each treatment group were compared using a Chi-squared test presenting odds ratios, 95% CIs and p-values. The number of rescue medication doses and the total mean amount was presented by treatment group;
- Non-Opioid Co-medication Use - The number of patients, doses and total amount of non-opioid analgesia co-medication were summarised by treatment group, and a Chi-squared test was performed;
- Patient Global Assessment - The number and percentages of patients who responded poor, fair, good or excellent were summarised at study drug discontinuation and converted to a binary variable of failure (including poor and fair) and success (including good and excellent). A logistic regression model was fitted with success/failure as the response variable and surgery type and treatment as model factors. A Mantel-Haenszel Chi-squared test was performed to compare the initial categories and binomial categories of the patient global assessment of pain control.

RESULTS:

Subject Disposition: Following the early suspension and termination of the study due to concerns regarding one batch of the study drug used outside this study and consideration there would be a substantial delay until the study could be resumed, which could have affected the continuity of the results, a total of 108 patients were randomised to study drug (58 to Ionsys and 50 to morphine IV PCA), and of those, 101 completed the study and completed study drug. Seven patients (6.5%) discontinued the study and study drug; 5 (8.6%) were in the Ionsys group and 2 (4.0%) were in the morphine IV PCA group. Of the 5 patients in the Ionsys treatment group, 4 (80.0%) discontinued study drug due to inadequate analgesia and use of rescue medications after the first 3 hours on operative day. One patient (20.0%) in the Ionsys group discontinued the study drug due to an AE of mild nonserious hypotension and somnolence that resolved. Of the 2 morphine IV PCA patients who discontinued the study and study drug, 1 patient (50.0%)

discontinued due to suspected technical failure and 1 patient (50.0%) discontinued due to other reasons (as specified on the CRF as 'Venflon tissued-not resited').

Demographics and Baseline Characteristics: Demographic characteristics were similar between patients in the Ionsys and morphine IV PCA groups. The majority of patients were female (33 [56.9%] Ionsys patients and 33 [66.0%] morphine IV PCA patients) and were Caucasian (57 [98.3%] Ionsys patients and 48 [96.0%] morphine IV PCA patients). Mean age was 58.4 years (SD=12.1 years; range: 36-86 years) for Ionsys patients and was 58.9 years (SD=11.8; range: 39-89 years) for morphine IV PCA patients. Mean weight was 81.8 kg (SD=16.8 kg; range: 51-137 kg) for Ionsys patients and was 80.6 kg (SD=18.2 kg; range: 53-146 kg) for morphine IV PCA patients. Mean height was 165.6 cm (SD=7.8 cm; range: 152-180 cm) for Ionsys patients and was 164.2 cm (SD=10.3 cm; range: 147-191 cm) for morphine IV PCA patients. The majority of patients in the Ionsys group had a BMI within 20-30 kg/m^2 (32 patients, 55.2%) and had a level II ASA status (46 patients, 79.3%), and the majority of patients in the morphine IV PCA group Ionsys group had a BMI within 20-30 kg/m^2 (30 patients, 60.0%) and had a level II ASA status (36 patients, 72.0%).

The majority of patients having an abdominal hysterectomy (ITT population; N=30) were Caucasian (28 patients, 93.3%). Mean age was 45.2 years (SD=6.5 years; range: 36-64 years). Mean weight among patients was 70.4 kg (SD=12.5 kg; range: 51-101 kg) and mean height was 159.2 cm (SD=5.0 cm; range: 150-170 cm). The majority of patients had a BMI within 20-30 kg/m^2 (22, 73.3%) and had a level II ASA status (19, 63.3%). Demographic characteristics were similar between patients having an abdominal hysterectomy in the Ionsys and morphine IV PCA groups. The majority of patients having hip arthroplasty (ITT population; N=78) were male (42, 53.8%) and were Caucasian (77 patients, 98.7%). Mean age was 63.8 years (SD=9.0 years; range: 42-89 years). Mean weight among patients was 85.4 kg (SD=17.3 kg; range: 53-146 kg) and mean height was 167.1 cm (SD=9.3 cm; range: 147-191 cm). The majority of patients had a BMI within 20-30 kg/m^2 or 30-40 kg/m^2 (75, 96.2%) and had a level II ASA status (63 patients, 80.8%). Demographic characteristics were similar between patients having hip arthroplasty in the Ionsys and morphine IV PCA groups.

Overall, the majority of patients (78 patients, 72.2%) had orthopaedic surgery, and the most common method of analgesia was a spinal anaesthetic of <4 hours duration of action (72 patients, 66.7%). The frequencies of type of surgery and method of analgesia were similar among the Ionsys and morphine IV PCA treatment groups.

Extent of Exposure: Overall, mean duration on treatment for all patients was 27.0 hours (SD=10.0 hours, range: 5-67 hours). Patients in the Ionsys treatment group stayed on study treatment longer than those in the morphine IV PCA group; the adjusted mean (95% CI) was 33.5 hours (30.0, 37.1 hours) for Ionsys patients and 28.4 hours (24.2, 32.6 hours) for morphine IV PCA patients. The adjusted mean difference (Ionsys - morphine IV PCA) with 95% CIs was 5.1 hours (1.8, 8.4 hours), showing a statistically significant difference (p=0.003) in patient duration on treatment for the 2 treatment groups.

Mean differences were similar for the abdominal hysterectomy and hip arthroplasty patients. The adjusted mean difference (Ionsys - morphine IV PCA) with 95% CIs was 4.7 hours (-2.0, 11.3 hours) for the abdominal hysterectomy patients, which was not statistically significant (p=0.159), and the adjusted mean difference (Ionsys - morphine IV PCA) with 95% CIs was 5.4 hours (1.6, 9.2 hours) for the hip arthroplasty patients, which was statistically significant (p=0.006).

Overall, Centre 4 (Liverpool) and Centre 2 (Cardiff) were the centres that had the longest duration on treatment for all patients, 29.3 hours (SD=8.7 hours, range: 24-47 hours) and 29.0 hours (SD=10.1 hours, range: 5-49 hours), respectively.

Doses for both the Ionsys and morphine IV PCA treatment groups increased during the study until the maximum permitted time at 72 hours, when only 1 patient in each group received a dose of study drug. For the entire study duration, mean total dose for the Ionsys group (n=58) was 1958 μg (SD=923.4 μg, range: 120-3720 μg) and mean total dose for the morphine IV PCA group (n=49) was 41.0 mg (SD=25.4 mg, range: 4-108 mg).

For System 1 (ie, the first system to be used), the majority of patients in the Ionsys group (46, 82.1%) had the transdermal PCA device placed on their left upper outer arm or left chest. For System 2, a similar number of patients had the transdermal PCA device placed at each location (ie, left upper outer arm, left chest, right upper outer arm, and right chest). For System 3, only 1 patient had the transdermal PCA device placed, which was on their right upper outer arm. All systems for all patients adhered to at least 90% of the area with no unattached edges.

Primary Efficacy

Ability to Mobilise: The adjusted mean (95% CI) ability to mobilise score at the time patients stopped study drug was 0.14 (-0.19, 0.47) for Ionsys patients and 2.37 (1.98, 2.76) for morphine IV PCA patients. The adjusted mean difference (Ionsys – morphine IV PCA) with 95% CIs was -2.23 (-2.55, -1.91), with a p-value of <0.001 from the ANCOVA showing a statistically significant difference in the ability to mobilise at the time the patient stopped study drug for the two treatment groups. Patients in the Ionsys group had greater perceived ability to mobilise at the time of stopping study drug. Similar results were obtained from a sensitivity analysis based on Fisher's Exact test ($p<0.001$).

Secondary Efficacy

Ability to Mobilise: Patients in the Ionsys group had greater perceived ability to mobilise at all time points; mean ability to mobilise scores for Ionsys patients were lower (ie, better) compared to morphine IV PCA patients at all time points. The ANCOVA analysis on the PP population confirmed the ITT population results. The difference between treatment groups was consistent across centres and surgery type. The confirmatory ANCOVA analysis re-run on the ITT Population with the duration of study treatment included as a covariate produced very similar results. However, the effect of time on study drug was not statistically significant (p=0.962).

Patient's Pain Rating: The analysis of the 72 hour time point was not done due to low or insufficient patient numbers. At 24 and 48 hours, the patient's pain rating was lower for Ionsys patients. At 24 hours, the adjusted mean (95% CI) pain rating was 1.97 (1.24, 2.70) for Ionsys patients and 2.46 (1.51, 3.41) for morphine IV PCA patients. The adjusted mean difference (Ionsys – morphine IV PCA) with 95% CIs was -0.49 (-1.29, 0.30), which was not statistically significant (p=0.219). At 48 hours, the adjusted mean (95% CI) pain rating was 0.39 (-0.47, 1.25) for Ionsys patients and 0.92 (-0.10, 1.95) for morphine IV PCA patients. The adjusted mean difference (Ionsys - morphine IV PCA) with 95% CIs was -0.53 (-1.59, 0.53), which was not statistically significant (p=0.299). At study discontinuation, the adjusted mean (95% CI) pain rating was 2.38 (1.38, 3.37) for Ionsys patients and 1.67 (0.59, 2.76) for morphine IV PCA patients. The adjusted mean difference (Ionsys – morphine IV PCA) with 95% CIs was 0.70 (-0.22, -1.63), which was not statistically significant (p=0.136).

Nurse EOC Questionnaire: Patients in the Ionsys group had a lower (ie, better) total score for the EOC questionnaire. The adjusted mean (95% CI) total EOC score was 0.28 (0.07, 0.49) for Ionsys patients and 0.80 (0.55, 1.05) for morphine IV PCA patients. The adjusted mean difference (Ionsys - morphine IV PCA) with 95% CIs was -0.52 (-0.74, -0.30), which showed a statistically significant ($p<0.001$) difference in total EOC score for the two treatment groups. Similar results to those obtained for the total EOC questionnaire score were obtained for the time consuming and the bothersome subsections of the EOC questionnaire ($p<0.001$), showing significantly better scores for Ionsys. The results from the satisfaction sub-section of the EOC questionnaire were not statistically significant for Ionsys versus morphine IV PCA treatment (p=0.922).

Time to FFD: A log-rank test stratified by surgery type was performed to compare the time to FFD for the two treatment groups. Fifty-four Ionsys patients (93.1%) and 50 morphine IV PCA patients (100.0%) achieved FFD. The median (95% CI) time to FFD was 70.08 hours (65.50, 72.25 hours) for Ionsys patients, and 71.21 hours (67.42, 90.77 hours) for morphine IV PCA patients. The difference in FFD between the two treatment groups was not statistically significant (p=0.342). When the analysis was repeated by surgery type by centre and by both centre and surgery type, there was no evidence of a

statistically significant difference in time to FFD between Ionsys and morphine IV PCA patients (all p-values >0.05).

The hazard ratio (95% CI) for patients who had received pre-enrolment medication was 0.80 (0.54, 1.21) with a p-value of 0.297. The hazard ratio (95% CI) for patients who did not receive any pre-enrolment medication was 0.18 (0.04, 0.80) with Ionsys patients achieving FFD sooner than morphine patients, which was statistically significant (p=0.024). However, the assumptions of the Cox-proportional hazard model did not hold and proportionality could not be claimed.

Time to Achieve Mobility Sub-Scale Criteria: All p-values were produced using a stratified log-rank test; all were not statistically significant (p>0.05) except for time to adequate pain control (p=0.016). The median (95% CI) time to adequate pain control was 32.17 hours (29.42, 42.47 hours) for Ionsys patients and 26.00 hours (24.75, 27.62 hours) for morphine IV PCA patients. This does not imply that adequate pain control was achieved faster with one group, but rather that the morphine IV PCA group had study treatment discontinued earlier for whatever reason.

Overall, the difference between treatment groups in time to actual discharge was not statistically significant (p=0.836). However, when the results were presented by centre, the analysis performed on time to actual discharge for 1 centre (Centre 1, Edinburgh) showed a statistically significant difference between the two treatment groups (p=0.027); the median (95% CI) time to actual discharge was 85.38 hours (70.25, 97.17 hours) for Ionsys patients and 96.00 hours (93.57, 99.42 hours) for morphine IV PCA patients.

The adjusted mean difference (Ionsys – morphine IV PCA) for distance walked at the time the individual criterion was met with 95% CIs was 12.17 m (-8.17, 32.50 m), which was not statistically significant (p=0.238). The adjusted mean difference (Ionsys – morphine IV PCA) for the number of stairs climbed at the time the individual criterion was met with 95% CIs was 0.38 (-0.87, 1.63), which was not statistically significant (p=0.545).

PGA of Pain Control: Thirty one Ionsys patients (53.4%) and 19 morphine IV PCA patients (38.8%) gave a response of 'excellent'. The odds ratio (95% CI) comparing Ionsys and morphine IV PCA was 1.81 (0.84, 3.92), indicating that Ionsys patients were more likely to give a response of 'excellent'. However, the p-value of 0.131 was not statistically significant. When assessed by centre, the majority of patients in both treatment groups at all centres assessed their pain control as either 'excellent' or 'good'.

The binary categories for the PGA of pain control included the responses 'poor' and 'fair' ('failure') versus the response categories 'good' and 'excellent' ('success'); 52 Ionsys patients (89.7%) and 42 morphine IV PCA patients (85.7%) had a response of success, and 6 Ionsys patients (10.3%) and 7 morphine IV PCA patients (14.3%) had a response of failure. The odds ratio (95% CI) comparing Ionsys and morphine IV PCA was 1.44 (0.45, 4.63), indicating that Ionsys patients were more likely to give a response of 'good' and 'excellent' ('success'). However, the p-value of 0.536 was not statistically significant. When assessed by centre, similar results were seen with the majority of patients in both treatment groups at all centres assessing their pain control as either 'excellent' or 'good' ('success').

Use of Rescue Medication: A total of 12 patients (11.0%) required rescue morphine in the first 3 hours post-randomisation (10 patients [17.2%] in the Ionsys group and 2 [4.0%] in the morphine IV PCA group). The odds ratio (95% CI) comparing Ionsys and morphine IV PCA was 5.00 (1.04, 24.03), showing a statistically significant difference (p=0.029) in the number of patients receiving rescue medication post-randomisation, with Ionsys patients more likely to receive rescue medication.

The mean number of doses required in the first 3 hours post-randomisation was 2.0 (SD=1.7, range: 1-6) for Ionsys patients and 1.0 (range: 1-1) for morphine IV PCA patients. The adjusted mean amount of morphine required (95% CI) was 9.0 mg (4.5, 13.5 mg) for Ionsys patients and was 7.2 mg (-2.6, 17.0 mg) for morphine IV PCA patients. The adjusted mean difference (Ionsys - morphine IV PCA) with 95% CIs was 1.8 (-6.8, 10.5), which was not statistically significant (p=0.624).

Use of Antiemetic Medication: In total, 55 patients (51.0%) used concomitant antiemetic medication during the study (29 Ionsys patients [50.0%] and 26 morphine IV PCA patients [52.0%]). Overall, there were no discernible differences in the use of concomitant antiemetic medication between the two treatment

groups. The most commonly used (≥10 patients in either treatment group) were cyclizine (39 patients [36.0%]; 19 Ionsys patients [33.0%] and 20 morphine IV PCA patients [40.0%]) and ondansetron (23 patients [21.0%]; 11 Ionsys patients [19.0%] and 12 morphine IV PCA patients [24.0%]).

Non-Opioid Analgesics: Forty-eight Ionsys (82.8%) and 36 morphine IV PCA patients (72.0%) received post-operative non-opioid analgesics. The odds ratio (95% CI) comparing Ionsys and morphine IV PCA was 1.87 (0.74, 4.68), indicating that Ionsys patients had been more likely to receive post-operative non-opioid analgesics. However, the p-value of 0.180 was not statistically significant. Thirty-nine Ionsys (67.2%) and 28 morphine IV PCA patients (56.0%) received post-operative paracetamol; the difference between the two groups was not statistically significant (p=0.230). Thirty-one Ionsys (53.4%) and 20 morphine IV PCA patients (40.0%) received post-operative NSAIDs; the difference between the two groups was not statistically significant (p=0.163). No patients in either treatment group received post-operative Cox-2 inhibitors.

Overall, a slightly larger proportion of Ionsys patients (40 patients [69.0%]) received intra-operative non-opioid analgesics when compared to morphine IV PCA patients (38 morphine IV PCA patients [76.0%]). The odds ratio (95% CI) comparing Ionsys and morphine IV PCA was 0.70 (0.30, 1.65), and the p-value of 0.416 was not statistically significant. Thirty-eight Ionsys (65.5%) and 35 morphine IV PCA patients (70.0%) received intra-operative paracetamol; the difference between the two groups was not statistically significant (p=0.620). Sixteen Ionsys (27.6%) and 24 morphine IV PCA patients (48.0%) received intra-operative NSAIDs; the difference between the two groups was statistically significant (p=0.028). One morphine IV PCA patient (2.0%) received intra-operative Cox-2 inhibitors.

SAFETY RESULTS:

Adverse Events: A summary of AEs is provided in Table 1.

Table 1. Summary of Adverse Events (Safety Population)

Number (%) of Patients	Ionsys (N=58)	Morphine IV PCA (N=50)	Overall (N=108)
Number of patients with at least 1 treatment-emergent AE	40 (69.0)	38 (76.0)	78 (72.2)
Number of patients with at least 1 treatment-related treatment-emergent AE	29 (50.0)	21 (42.0)	50 (46.3)
Number of deaths	0	0	0
Number of patients with at least 1 treatment-emergent SAE	1 (1.7)	2 (4.0)	3 (2.8)
Number of patients with at least 1 treatment-related treatment-emergent SAE	0	0	0
Number of withdrawals due to treatment-emergent AEs	5 (8.6)	1 (2.0)	6 (5.6)
Number of patients with at least 1 severe treatment-emergent AE	7 (12.1)	0	7 (6.5)

The two most common body classes for all treatment-emergent AEs were gastrointestinal (50 patients [46.0%]; 25 Ionsys patients [43.0%] and 25 morphine IV PCA patients [50.0%]) and vascular (33 patients [31.0%]; 18 Ionsys patients [31.0%] and 15 morphine IV PCA patients [30.0%]). Among all treatment-emergent AEs reported, nausea (32 patients [30.0%]; 19 Ionsys patients [33.0%] and 13 morphine IV PCA patients [26.0%]) and hypotension (27 patients [25.0%]; 14 Ionsys patients [24.0%] and 13 morphine IV PCA patients [26.0%]) had the highest incidence rates. Nausea (30 patients overall [28.0%]) and hypotension (9 patients overall [8.0%]) were the most common treatment-emergent treatment-related AEs as well.

Seven patients (12.1%) in the Ionsys group experienced treatment-emergent treatment-related application site AEs; 5 patients (8.6%) experienced application site erythema and 2 patients (3.4%) experienced application site vesicles. All application site AEs were mild in severity and resolved without medical intervention.

Non-Routine Events: Overall, 27 patients (25.0%) had at least 1 non-routine event (17 Ionsys patients [29.3%] and 10 morphine IV PCA patients [20.0%]). Ionsys patients were more likely to experience a non-routine event; however, the difference was not statistically significant (p=0.265).

A smaller proportion of Ionsys patients had their pain control interrupted due to a non-routine event. Overall, 3 Ionsys patients (5.2%) and 8 morphine IV PCA patients (16.0%) had their pain control interrupted; this difference almost reached statistical significance (p=0.064). Mean duration of pain control interruption for all patients was 119.3 minutes (SD=168.38 minutes; range: 5-600 minutes); mean duration of pain control interruption for the Ionsys group was three times lower than duration for morphine IV PCA patients (76.7 minutes [SD=80.83 minutes; range: 30-170 minutes] vs 135.3 minutes [SD=91.0 minutes; range: 5-600 minutes], respectively).

Blood Pressure, Heart Rate, Respiratory Rate, and Physical Findings: Decreases in mean diastolic and systolic BP from baseline to end of study were observed for both treatment groups combined (-12.4 mmHg [SD=13.9 mmHg] and -17.3 mmHg [SD=27.8 mmHg] for diastolic and systolic BP, respectively). Increases in mean heart rate were observed from baseline to end of study for both treatment groups combined (5.3 bpm [SD=13.7 bpm]). Slight decreases in respiratory rate were observed from baseline to end of study for both treatment groups combined (-0.1 breaths per minute [SD=3.0]).

The highest incidence of significant changes in vital signs occurred at Hour 3 (6 patients) in the overall population. Only 1 patient had a significant change in vital signs at the FFD visit, and 2 patients (1 in the Ionsys group and 1 in the morphine IV PCA group) had significant changes at end of study.

Prior and Concomitant Therapies: In total, 103 patients (95.0%) used therapies prior to the study (55 Ionsys patients [95.0%] and 43 morphine IV PCA patients [86.0%]). The most common therapies (used by ≥10 patients in either treatment group) included cefuroxime (79 patients [73.0%]; 41 Ionsys patients [71.0%] and 38 morphine IV PCA patients [76.0%]), propofol (79 patients [73.0%]; 42 Ionsys patients [72.0%] and 37 morphine IV PCA patients [74.0%]), paracetamol (72 patients [67.0%]; 35 Ionsys patients [60.0%] and 37 morphine IV PCA patients [74.0%]), bupivacaine (65 patients [60.0%]; 34 Ionsys patients [59.0%] and 31 morphine IV PCA patients [62.0%]), fentanyl (63 patients [58.0%]; 35 Ionsys patients [60.0%] and 28 morphine IV PCA patients [56.0%]), and midazolam (60 patients [56.0%]; 32 Ionsys patients [55.0%] and 28 morphine IV PCA patients [56.0%]).

In total, 106 patients [98.0%] used concomitant therapies during the study (56 Ionsys patients [97.0%] and 50 morphine IV PCA patients [100.0%]). The most common therapies (used by ≥10 patients in either treatment group) included paracetamol (59 patients [55.0%]; 36 Ionsys patients [62.0%] and 23 morphine IV PCA patients [46.0%]), tramadol (57 patients [53.0%]; 26 Ionsys patients [45.0%] and 31 morphine IV PCA patients [62.0%]), diclofenac (43 patients [40.0%]; 28 Ionsys patients [48.0%] and 15 morphine IV PCA patients [30.0%]), and cyclizine (40 patients [37.0%]; 20 Ionsys patients [34.0%] and 20 morphine IV PCA patients [40.0%]). However, no patient used concomitant oral opioids analgesia while on either study treatment, as per protocol.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION: This study demonstrates that Ionsys is significantly superior in its potential to enable patients to mobilise post-surgery whilst still enjoying continuous access to effective post-operative analgesia. Ionsys was effective and well tolerated in the management of acute moderate to severe post-operative pain. The study showed comparable efficacy between two treatment models and demonstrated a broadly similar tolerability profile. In addition, the results of the curtailed study indicate that the Ionsys system, whilst not reaching statistically significant levels of difference, may offer possible clinically significant and meaningful benefits to certain patients in relation to factors affecting FFD, a proxy for accelerated recovery and reduced hospital residence times. Given the drive in Western healthcare systems to reduce hospital residence times and promote accelerated recovery in post-surgical patients, the Ionsys system may contribute advantages to certain patients as being part of a component of an accelerated post-operative recovery initiative, alongside recognised approaches such as effective analgesia and encouraging post-operative enteral feeding.

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