25 January 2018
EMA/78915/2018
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) no 1901/2006

IONSYS

fentanyl

Procedure no: EMEA/H/C/002715/P46/003.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On the 29/06/2016 the MAH submitted a completed paediatric study for IONSYS 40 micrograms per dose transdermal system, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the specific obligation(s).

A short critical expert overview has also been provided.

IONSYS® is an iontophoretic transdermal system providing on-demand systemic delivery of fentanyl for up to 80 doses over 24 hours that was approved by the EMA in November 2015 (EU/1/15/1050/001)

In the European Union (EU), IONSYS® is indicated for the management of acute moderate to severe post-operative pain in adult patients.

2. Scientific discussion

2.1. Information on the development program

The results of study PD2013-002 are submitted as per Article 46 of Regulation (EC) No 1901/2006. In line with the European Medicines Agency (EMA) post-authorisation procedural advice for users of the centralised procedure, this Article 46 paediatric study submission is submitted as a post-approval measure. This study is part of the IONSYS® Paediatric Investigation Plan (PIP) EMEA-001509-PIP01-13-M01, study number 1369672683823 (EudraCT: 2014-002405-37).

The objective of the PD2013-002 study was to evaluate the safety and clinical utility of the active SSEC fentanyl 40 µg for the management of acute postoperative pain in paediatric subjects from 12 to less than 18 years of age.

The MAH stated that, based on the results of this study and in accordance with Article 16(2) of Regulation (EC) No 726/2004, the MAH states that the data submitted do not influence the benefit risk balance for IONSYS® and plans to update the IONSYS® European Union (EU) summary of product characteristics (SmPC) to include information about the adolescent population in the first quarter of 2018.

2.2. Information on the pharmaceutical formulation used in the study

The study systems used in this study are self-adhesive, single-use iontophoretic transdermal systems that provide up to 80 doses (40 µg each) of fentanyl per activation over 24 hours, on-demand. Each on-demand dose is delivered over a 10-minute period. The systems are comprised of two parts, a Drug Unit and a Controller, that are snapped together by the healthcare professional prior to use (Figure 1). The Controllers contain electronics that are pre-programmed to provide a direct current of 170 µA for 10 minutes upon activation. The Drug Unit contains 2 hydrogel reservoirs (anode hydrogel contains 10.8 mg fentanyl hydrochloride; cathode hydrogel contains 0.2% cetylpyridinium chloride), each 2.75 cm2 in area. The investigational label on the package containing each study system contained the protocol number, directions, and the usual caution and warning statements, and was in accordance with US regulatory requirements.

All subjects received lot #401428.

Figure 1: IONSYS® Separated System with Enhanced Controller (SSEC)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

• "*An Open Label Evaluation of the Safety and Clinical Utility of the Active, Separated System with Enhanced Controller (SSEC) Fentanyl 40 mcg for the Management of Acute Postoperative Pain in Paediatric Patients 12 to Less Than 18 Years of Age/PD2013/002* ".

2.3.2. Clinical study

Clinical study number and title

Study No: PD2013/002

Study Title:

An Open Label Evaluation of the Safety and Clinical Utility of the Active, Separated System

with Enhanced Controller (SSEC) Fentanyl 40 mcg for the Management of Acute Postoperative Pain in Paediatric Patients 12 to Less Than 18 Years of Age/PD2013/002 .

Sponsor:

Incline Therapeutics, Inc., a wholly owned subsidiary of The Medicines Company 900 Saginaw Drive, Suite 200 Redwood City, CA 94063 USA. Phone: (650) 241-6800

Investigators/ Sites:

Arjunan Ganesh, MD, Children's Hospital of Philadelphia; Mihaela Visoiu, MD, Children's Hospital of Pittsburgh of UPMC; Elliot Krane, MD, Stanford University School of Medicine; Anshuman Sharma, MD, Washington University in St. Louis; Sanjay Bhananker, MD, FRCA, Harborview Medical Center; Myron Yaster, MD, Johns Hopkins Hospital; Alan Farrow-Gillespie, MD, UT Southwestern Medical Center;

Steven Weisman, MD, Children's Hospital of Wisconsin; Michael Schmitz, MD, Children's Hospital of Atlanta; Andres Missair, MD, University of Miami Health System

Start Date: 29 June 2015 End Date: 12 Sept 2016

The Applicant states that this study was conducted in compliance with Good Clinical Practice (GCP) and protection of the subjects as required by the regulations and directives in operation at the time, including the archival of essential documents.

Description

Methods

Objective(s)

Core study

Primary Objective:

The objective of this study was to evaluate the safety and clinical utility of the active, separated system with enhanced controller (SSEC) fentanyl 40 µg for the management of acute postoperative pain in paediatric subjects 12 to less than 18 years of age.

Endpoints to Evaluate Clinical Utility:

The endpoints used to evaluate clinical utility were:

- Assessment of subject's ability to use the SSEC
- Assessment of adherence of the SSEC system

Endpoints to Evaluate Pharmacokinetics/Pharmacodynamics:

The endpoint used to evaluate pharmacokinetics (PK) was assessment of serum fentanyl concentration at each time point.

Endpoints for Other Analyses

- Pain intensity score over time including prior to administration of rescue medication timepoint
- Patient, parent/guardian, and investigator global assessments at each of the pre-specified study timepoints
- Opioid rescue medication
- Number of SSEC doses delivered
- Duration of fentanyl exposure

Safety Endpoints

Endpoints for safety analyses included

- Changes in vital signs from baseline, including CRRD
- Changes in the skin irritation score from baseline
- Incidence of adverse events(AEs)and SAEs

Study design

This was a Phase IIIb, multi-center, single-arm, open-label study to evaluate the safety and clinical utility of fentanyl 40 µg transdermal system in paediatric subjects from 12 to less than 18 years of age who had undergone general or regional anaesthesia for abdominal, pelvic/genitourinary, orthopaedic, or thoracic surgery who were screened between 3 weeks prior to surgery and the time of hospital admission.

Subjects received the active SSEC fentanyl iontophoretic transdermal system 40 µg for up to 3 consecutive days (up to 72 hours).

Postoperatively, subjects were to be observed during their recovery and titrated with an intravenous (IV) opioid, if clinically indicated, in order to achieve analgesic comfort (defined as having a pain intensity score ≤4 on the NRS from 0–10) for at least 30 minutes.

Upon application of the IONSYS® SSEC, an IV opioid would only be given as rescue medication. First line of choice was IV fentanyl, with IV morphine as a second line of choice.

Once a subject's pain intensity was ≤4 on the NRS for at least 30 minutes during recovery and the subject was awake, able to answer questions and follow commands, he/she was to be assessed for pain intensity, vital signs, and oxygen (O2) saturation. If the subject met the postoperative eligibility criteria, then additional baseline assessments (pain intensity, vital signs, and O2 saturation) were assessed prior to the start of the treatment period.

The start of the treatment period (i.e., Hour 0) began at the time the SSEC system was first assembled and applied to the subject's intact non-irritated skin on the chest or upper outer arm.

At the time of application of the first SSEC system, the subject was to be reinstructed on how to use the SSEC system. Only the subject was allowed to operate the SSEC system.

As needed, the subject could continue to use the SSEC for up to 72 hours. Each SSEC system was to be removed at the completion of every 24-hour SSEC treatment period or when 80 doses had been administered from the system, whichever occurred first, and a new SSEC system applied to a different location.

Key Inclusion Criteria

1. Subjects whose parent(s) or guardian(s) signed and dated an informed consent form for the subject to participate in the study, or subjects who provided written assent to participate in the study.

2. Male or female inpatients, age 12 to <18 years of age inclusive on the day of surgery.

3. Subjects capable of understanding and cooperating with the requirements of the study, including being able to report their pain intensity using the 11-point NRS and operate the SSEC.

4. American Society of Anaesthesiologists (ASA) physical status I, II, or III.

5. Body weight of at least 40.0 kg.

6. Postoperative subjects who had undergone general or regional anaesthesia for abdominal, pelvic/genitourinary, orthopaedic, or thoracic surgery.

7. Postoperative subjects who were observed during recovery and were expected to remain hospitalized and have pain requiring parenteral opioids (i.e., IV PCA) for the next 24 hours or longer.

8. Subjects who were awake and breathing spontaneously with a respiratory rate of 14 to 18 breaths per minute, peripheral capillary oxygen saturation (SpO2) ≥93% (with or without supplemental oxygen), and able to answer questions and follow commands.

9. Subjects who were observed during recovery, who were awake, able to answer questions and follow commands, and who were comfortable for at least 30 minutes, with a pain intensity score ≤4 (numeric rating scale 0–10), with or without titration to comfort with IV opioids.

<u>Key Exclusion Criteria</u>

1. Subjects who had undergone any surgery on the airway, head, or neck.

2. Subjects who received an extended-release opioid within 48 hours prior to Hour 0 or who were expected to have postoperative analgesia supplied by a continuous regional technique or patient-controlled epidural analgesia.

3. Subjects with a history of allergy or hypersensitivity to fentanyl, skin adhesives, and/or cetylpyridinium chloride.

4. Subjects who were expected to require intensive care or would likely require additional surgical procedures within 36 hours.

5. Subjects who received intraoperative and/or postoperative administration of opioids other than morphine, hydromorphone, fentanyl, sufentanil, or alfentanil. Exception: If there were no medical contraindications, meperidine (pethidine) up to 0.5 mg/kg IV was permitted during recovery for shivering.

6. Subjects who required airway support (nasal or oropharyngeal airway intubation, or laryngeal mask airway [LMA]) at the time of final baseline assessments (i.e., at the time of IONSYS® application [Hour 0]).

7. Subjects who were known or suspected to be opioid tolerant, have a history of opioid dependence within 3 months before the start of the study, or who were known to have used illicit drugs or alcohol within 14 days of the start of the study.

8. Subjects with active generalized skin disorders or active local skin disease that precluded SSEC application to the chest or upper arm.

9. Subjects with any coexisting major medical conditions likely to interfere with study procedures including, but not limited to, psychiatric conditions, chronic depression, suicidal ideation, autism.

10. Positive pregnancy test for any female.

Study population / Sample size

A sample size of at least 60 pediatric subjects was planned for this study in order to provide 95% confidence to detect AEs with at least 5.0% population event rate. A total of 71 subjects were enrolled, of whom 9 (12.7%) were screen failures. The Safety population included 61 subjects who received study intervention. Of these, 59 (96.7%) subjects completed the study, 1 (1.6%) withdrew consent, and 1 (1.6%) was lost to follow-up.

Table 4: Summary of Subject Disposition – Enrolled Population

Subject Disposition	SSEC Fentanyl 40 µg (N = 71) n (%)
Enrolled	71 (100.0)
Screening failure	9 (12.7)
Inclusion criteria not net	3 (4.2)
Exclusion criteria met	4 (5.6)
Subject/Parent/Investigator withdrawal of consent	1 (1.4)
Other	1 (1.4)
Safety Population[1*]	61 (85.9)
Completed study	59 (96.7)
Discontinued	2 (3.3)
Withdrew consent	1 (1.6)
Lost to follow-up	1 (1.6)

Source: Table 14.1.1.1.

[1] The Safety population includes all subjects who were enrolled and received at least one dose of fentanyl from the SSEC. Percentages are based on the number of patients enrolled. Number of patients in the Safety population is the denominator for percentages for the rest of the table.

* Subject 101001026 had IONSYS® application but with 0 dose.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller.

Demographic characteristics:

Overall, more subjects were female (73.8%) than male (26.2%). The mean age was 14.7 years (range: 12–17). Subjects were predominantly White (78.7%). The mean BMI was 22.3 kg/m2 (range: 16.4–42.1), with mean BSA 1.7 m2 (range: 1.3–2.4). Most subjects had an ASA physical status of class I (23.0%) or II (68.9%), indicating that they were healthy or only mild systemic disease was present.

Table 8: Demographic and Baseline Characteristics – Safety Population

Characteristics	SSEC Fentanyl 40 µg (N = 61)
Sex, n (%)	
Male	16 (26.2)
Female	45 (73.8)
Age (year)	
Mean (SD)	14.7 (1.54)
Median	15.0
Minimum, maximum	12.0, 17.0
Race, n (%)	
White	48 (78.7)
Black or African American	11 (18.0)
Asian	1 (1.6)
American Indian or Alaskan Native	1 (1.6)
Ethnic origin, n (%)	
Hispanic or Latino	4 (6.6)
Not Hispanic or Latino	57 (93.4)
Weight (kg)	
Mean (SD)	60.9 (17.75)
Median	56.3
Minimum, maximum	42.5, 131.8
Height (cm)	
Mean (SD)	165.1 (8.88)
Median	163.8
Minimum, maximum	148.0, 195.0
BMI (kg/m^2)	
Mean (SD)	22.3 (5.85)
Median	20.0
Minimum, maximum	16.4, 42.1
BSA (m^2)	
Mean (SD)	1.7 (0.23)
Median	1.6
Minimum, maximum	1.3, 2.4

Table 10: Surgical Procedure – Safety Population

Characteristic	SSEC Fentanyl 40 µg (N = 61)
Surgery, n (%)	
Abdominal	10 (16.4)
Cholecystectomy	4 (6.6)
Explorative laparotomy	1 (1.6)
Ileostomy closure	1 (1.6)
Laparoscopic surgery	1 (1.6)
Laparotomy	1 (1.6)
Ovarian cystectomy	1 (1.6)
Pancreatectomy	1 (1.6)
Orthopaedic	49 (80.3)
Spinal fusion surgery	42 (68.9)
Open reduction of fracture	3 (4.9)
Intramedullary rod insertion	1 (1.6)
Joint arthroplasty	1 (1.6)
Osteotomy	1 (1.6)
Tendon transfer	1 (1.6)
Pelvic/Genitourinary	1 (1.6)
Ovarian cystectomy	1 (1.6)
Thoracic	1 (1.6)
Cyst removal	1 (1.6)

Source: Table 14.1.4.1

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SD = standard deviation of the mean; SSEC = separated system with enhanced controller.

CHMP comment:

The study design is acceptable to describe safety and clinical utility.

A total of 71 subjects were screened for entry into the study. Of the subjects who were screened 61 were eligible to continue in the study and received the study drug. Of these, 59(96.7%) completed the study. One subject (1.6%) withdrew consent and one subject (1.6%) was lost to follow up.

During the study, 61 subjects received the study intervention. Overall, the number (percentage) of subjects who completed therapy was 59 (96.7%).

The mean age was 14.7 years (range: 12–17). There was a prevalence of female (73.8%) compared to male (26.2%). The White race represented 78.7% of the population; the Blacks or African American 18%; the Asians, American Indian and Alaskan Americans were the 1.6%The mean BMI was 22.3 kg/m2 (range: 16.4–42.1), with mean BSA 1.7 m2 (range: 1.3–2.4).

Most subjects had an ASA physical status of class I (23.0%) or II (68.9%), indicating that they were healthy or only mild systemic disease was present.

The choice of study population is adequate.

Treatments

Table 14: Number of SSEC Doses Delivered – Safety Population

Statistic	SSEC Fentanyl 40 µg (N = 61)
Number of SSEC fentanyl 40 µg applications, n (%)	
1	21 (34.4)
2	34 (55.7)
3	6 (9.8)

Statistic	SSEC Fentanyl 40 µg (N = 61)
Number of SSEC systems used	107
Number of on-demand doses delivered per SSEC	
Mean (SD)	23.9 (13.84)
Median	22.0
Minimum, maximum	1, 70
1–5	4 (3.7)
6–10	13 (12.1)
11–20	31 (29.0)
21–30	29 (27.1)
31–40	18 (16.8)
41–50	7 (6.5)
51–60	3 (2.8)
61–70	2 (1.9)
Number of on-demand doses delivered per subject	
Mean (SD)	41.9 (28.66)
Median	36.0
Minimum, maximum	1.0, 133.0

Source: Table 14.1.8.1.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SD = standard deviation of the mean; SSEC = separated system with enhanced controller.

Table 15: Duration of Fentanyl Exposure – Safety Population

Statistic	SSEC Fentanyl 40 µg (N = 61)
Duration of fentanyl exposure (hours)	
Mean (SD)	36.1 (16.23)
Median	41.8
Minimum, maximum	0.2, 71.7

Source: Table 14.1.8.1.

Abbreviations: N = number of subjects in the specified group; SD = standard deviation of the mean; SSEC = separated system with enhanced controller.

A total of 21 (34.4%) subjects had 1 application, 34 (55.7%) subjects had 2 SSEC applications, and 6 (9.8%) subjects had 3 applications. The mean number of on-demand doses delivered from the 107 SSECs was 23.9, and the mean number of on-demand doses delivered per subject was 41.9.

Mean duration of Fentanyl exposure was 36.1 hours.

Statistical Methods

STUDY POPULATIONS

Three patient populations were considered in the statistical analyses of this study.

SAFETY POPULATION

All subjects who receive at least one dose of fentanyl from the SSEC. This was the primary population used for the safety analysis.

EVALUABLE POPULATION

All subjects who received fentanyl from the SSEC for at least 3 hours. This was the primary population for the analysis on utility assessments, pain intensity and global assessments.

PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) POPULATION

All subjects who are treated and have at least one blood sample collected after study drug administration. This will be the primary population for PK/PD analysis.

GENERAL STATISTICAL METHODOLOGY

Patient disposition, demographic and background characteristics were to be presented for the safety, evaluable and PK/PD populations. Unless otherwise specified, all utility assessment, pain intensity, and global assessments analyses were to be performed using the evaluable population, all safety analyses were to be performed using the safety population and all PK/PD analyses were to be performed using the PK/PD population.

Continuous variables was summarized using descriptive statistics including the number of subjects reflected in the calculation (n), mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum (min), and maximum (max).

Frequencies and percentages were displayed for categorical variables. For PK parameters, percent of coefficient of variation (%CV) is also be presented.

Because of the descriptive nature of this study, no formal statistical hypothesis testing was performed. However, two-tailed 95% confidence intervals were generated to demonstrate the strength of the findings whenever appropriate.

The observational period for the study includes screening (within 21 days prior to surgery) through 7 days following end of study drug administration. Any event occurring after the defined observational period, even if collected on the CRF, was not be included

Unless otherwise specified for repeat pre-baseline assessments, the results from the final assessment made before or at the start of SSEC were used as baseline. If post-baseline assessments were repeated or unscheduled, the non-missing values from the first assessment were used for generating summary statistics.

Unless otherwise specified, missing data were not imputed and were excluded from the associated analysis.

SAFETY ANALYSES

The safety data, including AEs/SAEs, opioid-related AEs from the time of application of the first system through 7 days following end of study drug administration, vital signs from 0 to 72 hours (at Screening, Hour 0 (i.e., before system application), and 30 minutes, Hours 1, 2, 3, 4, 6, 8, 10, and 12 after system application, and every 4 hours thereafter until 72 hours or early withdrawal occurs), as well as the changes in skin irritation score from baseline at 1 and 24 hours following removal of each system.

Opioid-related AEs include hypoventilation, hypoxia, hypotension, tachycardia, nausea, vomiting, constipation, ileus, urinary retention, somnolence, pruritus, confusional state, dyspnoea, and apnoea.

The following safety endpoints were analyzed:

• Changes in vital signs from baseline, including CRRD

• Changes in skin irritation score from baseline

• Incidence of adverse events (AEs) and serious adverse events (SAEs)

The MedDRA dictionary, version 18.0 was used for coding adverse events (AEs). An AE (classified as preferred term) occurring during the treatment period was counted as a treatment emergent AE (TEAE) either if it is was present at baseline or if it was present at baseline but increased in severity during the treatment period.

Vital signs include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature, O2 saturation and supplemental oxygen.

The number and percent of subjects reporting serious AE and TEAEs for each preferred term were tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to study drug. If more than one event occurred with the same preferred term for the same subject, the subject was counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively. Application site reaction (ASR) AEs were tabulated and summarized separately.

Listings are presented for subjects with SAEs/AEs leading to a discontinuation or death.

Respiratory function and occurrence of CRRD is defined as simultaneous occurrence of bradypnoea (respiratory rate < 10 breaths per minute for subjects 9-15 years of age and sustained for 1 minute, or <8 breaths per minute for subjects 16-17 years of age), with excessive sedation (i.e., the patient is not easily aroused). CRRD will be recorded and presented as an adverse event whenever it occurs.

Descriptive statistics for skin irritation score, vital signs at each collection timepoint are provided. Summary of change from baseline in vital signs and skin irritation score is presented at each collection time point.

ANALYSIS OF CLINICAL UTILITY

The following endpoints to assess clinical utility were analyzed:

• Assessment of subject's ability to use SSEC

• Assessment of adherence of the SSEC system

Assessments of the pediatric subject’s ability to use the SSEC system safely and effectively were completed at the time of the subject’s termination of study treatment by the investigator. The assessment consisted of a 4-level categorical evaluation (poor, fair, good, and excellent).

The adhesion of each SSEC system was evaluated immediately prior to removal at each 24-hour time point, or at early withdrawal. Adhesion was recorded using the following classification: System adhered to at least 90% of the application area with no edges unattached; System adhered between 75 and 89%; System was <75% adhered and not taped; System was secured with tape. Number and percentage of subjects in each category for both endpoints are presented.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

PRIMARY PK ANALYSIS

During the study, up to 5 blood samples were drawn to determine the serum fentanyl concentration at the following time points: 30 minutes prior to the application of the first system i.e. baseline (Hour 0), 3, 6, 12, and 24 hours following SSEC application.

Descriptive statistics for serum fentanyl concentration level at each of the pre-specified time point are provided.

The PK analysis will be explored using the patient population data at 3, 6, 12 and 24 hours from the application of the first SSEC system, respectively, to assess the effect of the dosing time on the systemic exposure of fentanyl.

The serum concentrations of fentanyl as a function of the derived PK time points were analyzed using standard noncompartmental analysis or nonlinear mixed-effects modelling if applicable. Cmax, Tmax, AUC, apparent volume of distribution, apparent of clearance, T1/2, MRT were calculated.

PK/PD RELATIONSHIP

All analysis for PK/PD relationship will be using PK/PD population. The following analyses will be performed for PK/PD relationship: The relationship between fentanyl serum concentration and pain intensity score using the Numeric Rating Scale (NRS) will be explored with Emax model. The relationship between fentanyl serum concentration and adverse events of interest (e.g., clinically relevant respiratory depression) will be explored with Emax model.

OTHER ANALYSES

The following endpoints were analysed:

• Pain intensity score over time including prior to administration of rescue medication timepoint

• Patient, parent/guardian, and investigator global assessments at each of the pre-specified study time points

• Opioid rescue medication, number of SSEC doses delivered, and duration of fentanyl exposure

Pain intensity score was measured using the 11-point Numeric Rating Scale (NRS)

from 0 =no pain to 10 = worst possible pain.

For pain intensity score, descriptive statistics including n, mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) will be provided at each of the pre-specified timepoint including end of study treatment. For any missing pain assessment at Hour 0 or at the end of study treatment, the last observation carry forward method will be used to impute the assessment using the value right before the timepoint.

The number and percent of subjects who achieve each category of global assessment (poor, fair, good, and excellent) as well as success versus failure of the SSEC at hours 24, 48, and 72 as well as the last

timepoint in study evaluated by patient, parent/guardian, and investigator will be presented along with their associated 95% confidence interval. Here

Hour 24 is defined as either assessment at Hour 24 or at the time of discharge if a subject is discharged before Hour 24. The evaluable population will be used as the primary population for Pain intensity and global assessment.

SUBGROUP ANALYSIS

The following subgroup analyses will be performed:

☐ Age groups;

The subgroup analysis will be descriptive.

CHMP comment:

The methods of analysis are descriptive which is appropriate for this type of study. However, safety is one of the main endpoints assessed and the safety population includes all patients dosed. This is appropriate but it needs to be born in mind that patients who stop treatment early may be less likely to report AEs after that. Hence the proportion of patients with certain AEs may be diluted by the inclusion of these subjects.

Results

Efficacy results

Analyses of Clinical Utility

The endpoints used to assess clinical utility for this study were assessment of the subject's ability to use the SSEC, and assessment of adherence of the SSEC system.

Assessment of Subject's Ability to Use SSEC

A rating of 'excellent' was assessed in 48 (78.7%) subjects, with an additional 10 (16.4%) subjects being assessed with a rating of 'good.' Only 3 (4.9%) subjects were assessed with ratings of 'fair' or 'poor.'

Table 11: Investigator's Assessment of Subject's Ability to Use the SSEC – Evaluable Population

Rating	SSEC Fentanyl 40 µg (N = 61) n (%)
Poor	1 (1.6)
Fair	2 (3.3)
Good	10 (16.4)
Excellent	48 (78.7)
Missing	0

Source: Table 14.2.5.1.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller.

Assessment of Adherence of the SSEC System

During the assessment period, 97 (90.7%) SSEC systems remained adhered to ≥90% of the area with no edges unattached. An additional 9 (8.4%) SSEC systems remained partially adhered, while only 1 (0.9%) required tape to secure it.

Table 12: Adherence of the SSEC System – Evaluable Population

Statistic	SSEC Fentanyl 40 µg (N = 61)
Number of Systems Used	107
Assessment of adherence of the SSEC system, n (%)	
≥90% of the area with no edges unattached	97 (90.7)
75% to 89%	6 (5.6)
<75% adhered and not taped	3 (2.8)
System was secured with tape	1 (0.9)
Not assessed	0

Source: Table 14.2.6.1.

Note: Denominator in calculations is the number of systems used.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller.

CHMPcomment

The assessment of the ability to use the SSEC system was rated 'excellent' in 78.7% of the subjects, 'good' in 16.4%, 'fair' in 3.3%(one 12 y.o. and one 14 y.o. subjects) and 'poor' in 1.6%(one 14 y.o. subject). The ability to use the system does not seem to be age -related.

The adherence of the system showed that during the assessment period (completion of 24-hour SSEC treatment period or when 80 doses have been administered from the system) 90.7% SSEC systems remained adhered to ≥90% of the area.

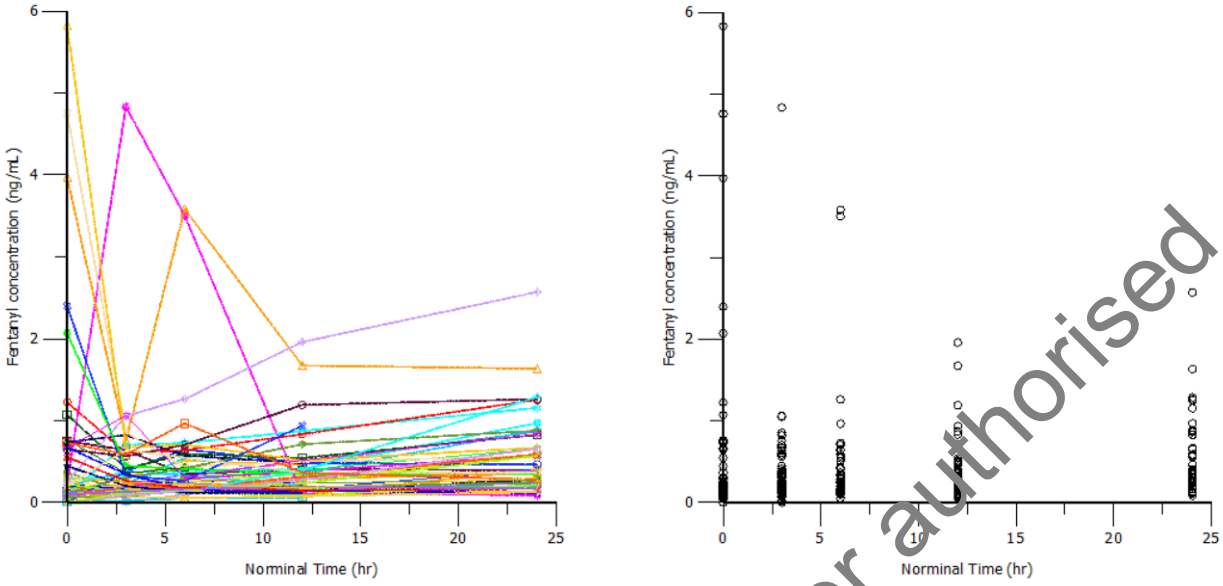
Pharmacokinetic/Pharmacodynamic Analyses

PK calculations included serum fentanyl concentrations at each time point.

A total of 59 subjects who were treated and had at least one out of the possible five blood samples collected for fentanyl PK were included in the PK/PD population. Of these, 51 subjects were pre-medicated with IV fentanyl and 8 subjects received no pre-medication; the pre-medication was intended to control pain in the immediate postoperative period and to titrate pain to comfort (NRS pain intensity score ≤4) prior to SSEC fentanyl application.

Individual concentration-time profiles and concentrations were plotted by nominal time (time between application of the first SSEC and PK blood sample) as well as Δt.

Figure 2: Individual Concentration-Time Profiles for Fentanyl with Nominal Time - PK/PD Population



As shown in Figure 2, two subjects showed high early fentanyl levels at 2.4 and 5.7 hours, respectively. Subject 2002 (concentration peak at 2.4 hours, magenta line) used the SSEC 8 times in the first 3 hours after SSEC placement, and then not again for the next 8 hours.

Subject 2009 (concentration peak at 5.7 hours, yellow line) used the SSEC 70 times during the 24 hours of SSEC placement, most frequently in the first 6 hours following SSEC placement.

One additional subject (Subject 2014, fuchsia line) used the SSEC 66 times during the 24 hours of SSEC placement, on average every 22 minutes over the 24 hour period, and showed steadily rising plasma concentrations of fentanyl. None of these 3 subjects received supplemental opioids during the SSEC treatment period.

Fentanyl concentrations were generally stable over the course of the study, with mean and median concentrations similar at all timepoints. Inter-subject variability in concentrations was fairly high, and likely associated with the individual titration of doses by each subject. Fentanyl concentrations upon placement of IONSYS® SSEC tended to be stable within individual subjects (i.e., intrasubject variability was low), as illustrated in Figure 5, and in individual subject listings.

Table 14.2.7.1 Serum Fentanyl Concentration Level (ng/mL) at each of the Pre-specified Time Point (PK/PD Population)

PK Timepoint	Statistics	SSEC Fentanyl 40 mcg (N=59)
0 Hr	N	59
	Mean (SD)	0.56 (1.113)
	Median	0.18
	Q1, Q3	0.09, 0.55
	Min, Max	0.0, 5.8
3 Hrs	N	55
	Mean (SD)	0.40 (0.660)
	Median	0.21
	Q1, Q3	0.15, 0.45
	Min, Max	0.0, 4.8
6 Hrs	N	55
	Mean (SD)	0.43 (0.655)
	Median	0.24
	Q1, Q3	0.14, 0.43
	Min, Max	0.1, 3.6
12 Hrs	N	58
	Mean (SD)	0.38 (0.355)
	Median	0.28
	Q1, Q3	0.17, 0.46
	Min, Max	0.1, 2.0
24 Hrs	N	43
	Mean (SD)	0.59 (0.483)
	Median	0.41
	Q1, Q3	0.27, 0.83
	Min, Max	0.1, 2.6

Data Source: Listing 16.2.04, 16.2.13.

Compound: Ionsys (PD2013-002), SAS Program: T-PC-SUM.SAS /Date: 06JUN2017 11:42

Table 14.2.7.1.1 Serum Fentanyl Concentration Level (ng/mL) by Age Group of the Pre-specified Time Point (PK/PD Population)

PK Timepoint	Statistics	12 yrs old (N=5)	13 yrs old (N=11)	14 yrs old (N=13)	15 yrs old (N=8)	16 yrs old (N=14)	17 yrs old (N=8)
0 Hr	N	5	11	13	8	14	8
	Mean (SD)	1.32 (1.964)	0.33 (1.140)	0.24 (0.338)	0.37 (0.697)	0.83 (1.562)	0.20 (0.233)
	Median	0.55	0.24	0.15	0.13	0.20	0.17
	Q1, Q3	0.12, 1.97	0.11, 0.75	0.08, 0.20	0.03, 0.27	0.11, 0.67	0.05, 0.21
	Min, Max	0.1, 4.8	0.0, 4.0	0.0, 1.2	0.0, 2.1	0.0, 5.8	0.0, 0.7
3 Hrs	N	4	10	12	7	14	8
	Mean (SD)	0.43 (0.299)	0.27 (0.246)	0.73 (1.327)	0.35 (0.347)	0.31 (0.180)	0.29 (0.281)
	Median	0.34	0.20	0.20	0.32	0.26	0.15
	Q1, Q3	0.22, 0.63	0.15, 0.36	0.16, 0.65	0.07, 0.45	0.18, 0.34	0.12, 0.43
	Min, Max	0.2, 0.9	0.0, 0.8	0.1, 4.8	0.1, 1.1	0.1, 0.7	0.1, 0.8
6 Hrs	N	5	10	13	7	14	6
	Mean (SD)	0.32 (0.186)	0.54 (1.076)	0.56 (0.909)	0.39 (0.408)	0.37 (0.261)	0.28 (0.211)
	Median	0.24	0.18	0.24	0.33	0.27	0.17
	Q1, Q3	0.17, 0.43	0.12, 0.34	0.16, 0.64	0.14, 0.41	0.16, 0.51	0.14, 0.54
	Min, Max	0.2, 0.6	0.1, 3.6	0.1, 3.5	0.1, 1.3	0.1, 1.0	0.1, 0.6
12 Hrs	N	5	10	13	8	14	8
	Mean (SD)	0.30 (0.199)	0.36 (0.474)	0.39 (0.237)	0.47 (0.611)	0.42 (0.327)	0.28 (0.127)
	Median	0.19	0.20	0.36	0.26	0.33	0.29
	Q1, Q3	0.14, 0.50	0.16, 0.38	0.19, 0.48	0.21, 0.38	0.18, 0.51	0.18, 0.36
	Min, Max	0.1, 0.5	0.1, 1.7	0.1, 0.9	0.1, 2.0	0.1, 1.2	0.1, 0.5
24 Hrs	N	5	6	10	7	9	6
	Mean (SD)	0.39 (0.293)	0.57 (0.539)	0.69 (0.433)	0.74 (0.850)	0.60 (0.347)	0.43 (0.287)
	Median	0.23	0.40	0.62	0.36	0.59	0.37
	Q1, Q3	0.17, 0.56	0.29, 0.57	0.36, 1.15	0.27, 0.97	0.28, 0.86	0.21, 0.66
	Min, Max	0.2, 0.8	0.1, 1.6	0.1, 1.3	0.1, 2.6	0.2, 1.3	0.1, 0.9

Data Source: Listing 16.2.04, 16.2.13.

Compound: Ionsys (PD2013-002), SAS Program: T-PC-SUM-AGE.SAS /Date: 06JUN2017 12:31

CHMP comment

Up to 5 blood samples were collected for measurement of serum fentanyl concentration during the first 24 hours: 30 minutes prior to application of the first system i.e baseline (Hour 0), then at 3, 6, 12, and 24-hour time points from the application of the first SSEC system.

The results show that the Individual Concentration-Time Profiles for Fentanyl were generally stable over the course of the study, with mean and median concentrations similar at all time points. Two subjects showed high early fentanyl levels at 2.4 and 5.7 hours, respectively. However, this seem related to the number of times the subjects used the SSEC system: Subject 2002 (concentration peak at 2.4 hours, magenta line) used the SSEC 8 times in the first 3 hours after SSEC placement, and then not again for the next 8 hours; Subject 2009 (concentration peak at 5.7 hours, yellow line) used the SSEC 70 times during the 24 hours of SSEC placement, most frequently in the first 6 hours following SSEC placement. The number and type of AEs reported by these two subjects doesn't differ from the rest of the group. No SAEs were reported.

It was noted that the Inter-subject variability in concentrations was quite high. The company justifies this variability with the different individual titration of doses by each subject. This justification seems reasonable and acceptable. However, intra-subject variability for Fentanyl concentrations was low and tended to be stable within individual subjects.

Other Analyses

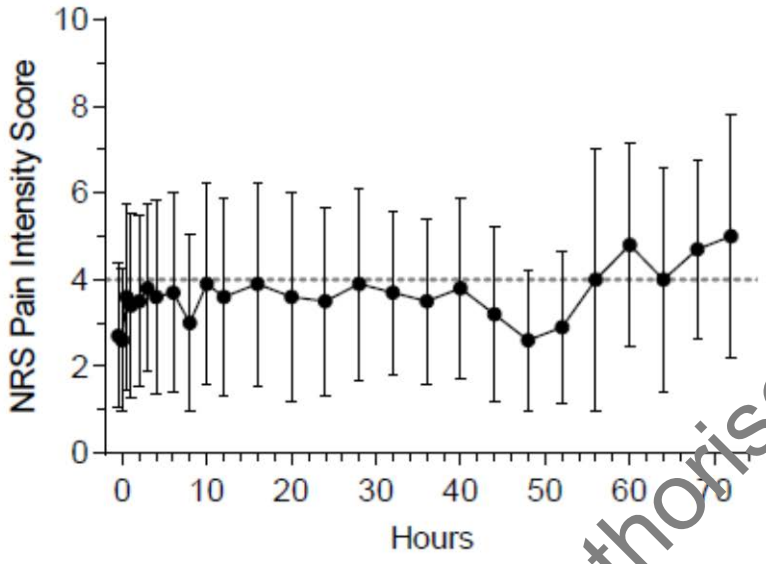
Pain Intensity Score Over Time

The analysis for pain intensity score over time was done by using the 11-point NRS.

After being titrated to a score of ≤4 prior to SSEC application, the mean NRS score remained ≤4 until 60 hours post-application (interpretation of scores showing continued control of pain on treatment at this and later time points are confounded by the fact that there were 4 or fewer subjects still using SSEC systems).

Figure 6: Numeric Rating Scale (NRS) Pain Intensity Score Over Time –

Evaluable Population

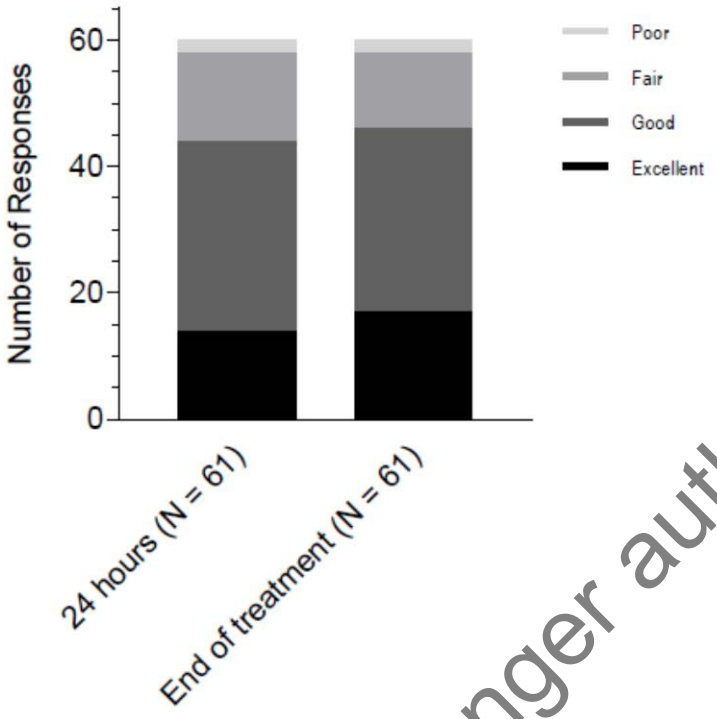


Source: Table 14.2.1.1.
Abbreviations: NRS = Numeric Rating Scale.

Patient Global Assessment

A rating of 'good' or 'excellent' (i.e., 'success' of the SSEC as a method of pain control) was reported by 44 (72.1%) subjects at 24 hours, and by 46 (75.4%) subjects at the end of treatment.

Figure 7: Patient Global Assessment – Evaluable Population



Source: Table 14.2.2.1.

Note: Patient Global Assessment at Hour 24 is defined as either assessment at Hour 24 or at the time of discharge if a subject is discharged before Hour 24.

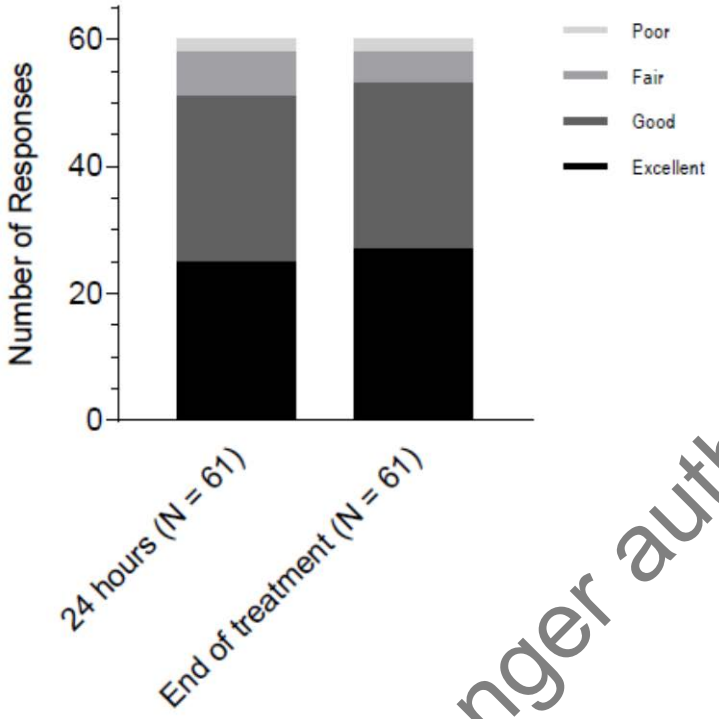
Mean duration of fentanyl exposure was 36.1 hours (Table 14); therefore the amount of data available is low after the assessment at 24 hours, due to discontinuation of IONSYS® SSEC and/or hospital discharge.

Abbreviations: N = number of subjects in the specified group.

Parent/Guardian Global Assessment

A rating of 'good' or 'excellent' (i.e., 'success' of the SSEC as a method of pain control) was reported by 51 (83.6%) parents/guardians at 24 hours, and by 53 (86.9%) parents/guardians at the end of treatment.

Figure 8: Parent/Guardian Global Assessment – Evaluable Population



Source: Table 14.2.3.1.

Note: Parent/Guardian Global Assessment at Hour 24 is defined as either assessment at Hour 24 or at the time of discharge if a subject is discharged before Hour 24.

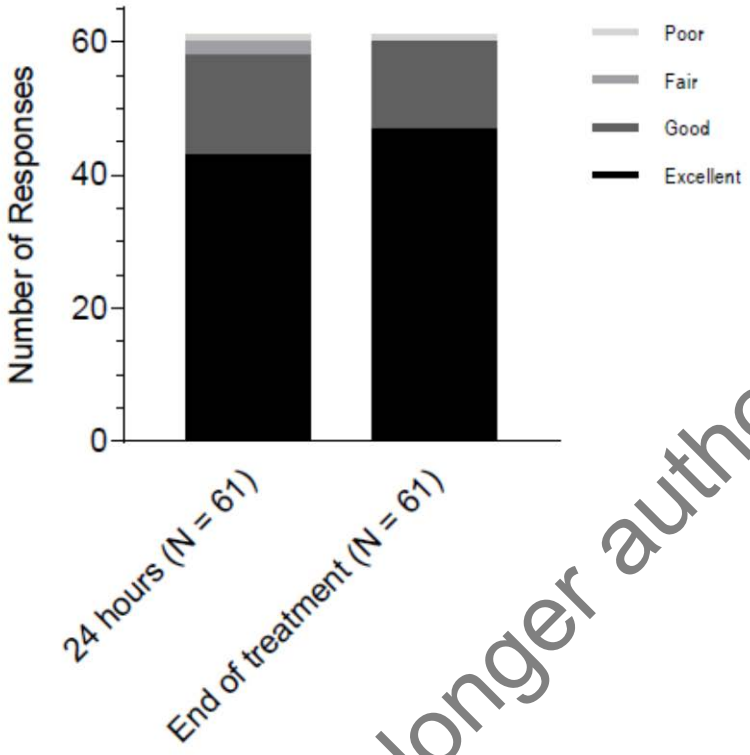
Mean duration of fentanyl exposure was 36.1 hours (Table 16); therefore the amount of data available is low after the assessment at 24 hours, due to discontinuation of IONSYS® SSEC and/or hospital discharge.

Abbreviations: N = number of subjects in the specified group.

Investigator Global Assessment

A rating of 'good' or 'excellent' (i.e., 'success' of the SSEC as a method of pain control) was reported for 58 (95.1%) subjects by the investigator at 24 hours, and for 60 (98.4%) subjects by the investigator at the end of treatment

Figure 9: Investigator Global Assessment – Evaluable Population



Source: Table 14.2.4.1.

Note: Investigator Global Assessment at Hour 24 is defined as either assessment at Hour 24 or at the time of discharge if a subject is discharged before Hour 24.

Mean duration of fentanyl exposure was 36.1 hours (Table 15); therefore the amount of data available is low after the assessment at 24 hours, due to discontinuation of IONSYS® SSEC and/or hospital discharge.

Abbreviations: N = number of subjects in the specified group.

Opioid Rescue Medication

Just over half of the subjects 29 (47.5%) received at least 1 rescue medication during the treatment.

Opioids were the most common rescue medication, used by 28 (45.9%) subjects. The most common opioid rescue medications used were hydromorphone in 19 (31.1%) subjects and oxycodone in 16 (26.2) subjects. Other rescue medications were used by fewer than 10% of subjects each.

Table 13: Rescue Medication, Including Opioid Rescue Medication, by Anatomic Therapeutic Chemical Classification – Evaluable Population

ATC Level 3 Preferred Term	SSEC Fentanyl 40 µg (N = 61) n (%)
Received at least one rescue medication	29 (47.5)
Antiinflammatory and antirheumatic products, non-steroidal	4 (6.6)
Ketorolac	4 (6.6)
Anxiolytics	5 (8.2)
Diazepam	5 (8.2)
Opioids	28 (45.9)
Hydromorphone	19 (31.1)
Morphine	2 (3.3)
Nalbuphine	1 (1.6)
Oxycodone	16 (26.2)
Oxycodone hydrochloride	1 (1.6)
Other analgesics and antipyretics	4 (6.6)
Gabapentin	3 (4.9)
Paracetamol	4 (6.6)

Source: Table 14.1.7.2.

Notes: The WHO Drug Dictionary Enhanced (September 2014 version) was used.

Abbreviations: ATC = Anatomic Therapeutic Chemical classification; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; WHO = World Health Organization.

Number of SSEC Doses Delivered

A total of 21 (34.4%) subjects had 1 application, 34 (55.7%) subjects had 2 SSEC applications, and 6 (9.8%) subjects had 3 applications. The mean number of on-demand doses delivered from the 107 SSECs was 23.9, and the mean number of on-demand doses delivered per subject was 41.9.

Table 14: Number of SSEC Doses Delivered – Safety Population

Statistic	SSEC Fentanyl 40 µg (N = 61)
Number of SSEC fentanyl 40 µg applications, n (%)	
1	21 (34.4)
2	34 (55.7)
3	6 (9.8)

Statistic	SSEC Fentanyl 40 µg (N = 61)
Number of SSEC systems used	107
Number of on-demand doses delivered per SSEC	
Mean (SD)	13.5 (13.84)
Median	22.0
Minimum, maximum	1, 70
1–5	4 (3.7)
6–10	13 (12.1)
11–20	31 (29.0)
21–30	29 (27.1)
31–40	18 (16.8)
41–50	7 (6.5)
51–60	3 (2.8)
61–70	2 (1.9)
Number of on-demand doses delivered per subject	
Mean (SD)	41.9 (28.66)
Median	36.0
Minimum, maximum	1.0, 133.0

Source: Table 14.1.8.1.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SD = standard deviation of the mean; SSEC = separated system with enhanced controller.

Duration of Fentanyl Exposure

Mean duration of fentanyl exposure (i.e., duration of application of the device to the skin) was 36.1 hours.

Table 15: Duration of Fentanyl Exposure – Safety Population

Statistic	SSEC Fentanyl 40 µg (N = 61)
Duration of fentanyl exposure (hours)	
Mean (SD)	36.1 (16.23)
Median	41.8
Minimum, maximum	0.2, 71.7

Source: Table 14.1.8.1.

Abbreviations: N = number of subjects in the specified group; SD = standard deviation of the mean; SSEC = separated system with enhanced controller

CHMP comment

For the measurement of 'Pain Intensity Score Over Time' the subjects were titrated to a score of ≤4 prior to SSEC application (with an intravenous opioid: IV Fentanyl as first line of choice and IV morphine as second line). The NRS score remained ≤4 until 60 hours post-application The Company states that 'interpretation of scores showing continued control of pain on treatment at this and later timepoints are confounded by the fact that there were 4 or fewer subjects still using SSEC systems'. This is acceptable.

The perception of 'success' of the SSEC as a method of pain control varies between patients ('good' or 'excellent' reported by 44 (72.1%) subjects at 24 hours, and by 46 (75.4%) subjects at the end of treatment); parent/guardians ('good' or 'excellent' reported by 51 (83.6%) at 24 hours, and by 53 (86.9%) at the end of treatment and Investigators ('good' or 'excellent' was reported for 58 (95.1%) subjects at 24 hours, and for 60 (98.4%) subjects at the end of treatment). However, the overall feeling of success is high.

At least one rescue medication was received by 29 (47.5%) subjects during the treatment. This indicates that almost half of the patients didn't have pain relief. However, since the study didn't include a comparator, it is difficult to comment on the efficacy of the product.

Opioids were the most common rescue medication, used by 28 (45.9%) subjects. The most common opioid rescue medications used were hydromorphone in 19 (31.1%) subjects and oxycodone in 16 (26.2) subjects. Other rescue medications were used by fewer than 10% of subjects each.

A total of 21 (34.4%) subjects had 1 SSEC application, 34 (55.7%) subjects had 2 SSEC applications, and 6 (9.8%) subjects had 3 applications. The mean number of on-demand doses delivered from the 107 SSECs was 23.9, and the mean number of on-demand doses delivered per subject was 41.9

Mean duration of fentanyl exposure (i.e., duration of application of the device to the skin) was 36.1 hours.

Discussion on efficacy

The assessment of efficacy was based on measuring the clinical utility of the active, separated system with enhanced controller (SSEC) fentanyl 40 µg for the management of acute postoperative pain in paediatric subjects 12 to less than 18 years of age.

The endpoints used to evaluate clinical utility were: Assessment of subject's ability to use the SSEC and Assessment of adherence of the SSEC system.

The assessment of the ability to use the SSEC system was rated 'excellent' in 78.7% of the subjects, 'good' in 16.4%, 'fair' in 3.3%(one 12 y.o. and one 14 y.o. subjects) and 'poor' in 1.6%(one 14 y.o. subject). The ability to use the system does not seem to be age -related. Overall it appears that the SSEC system is quite easy to use as it has been demonstrated by the feedback provided by the different age subgroups.

The adherence of the system showed that during the assessment period (completion of 24-hour SSEC treatment period or when 80 doses have been administered from the system) 90.7% SSEC systems remained adhered to ≥90% of the area.

For what concerns the PK analysis, the results show that the Individual Concentration-Time Profiles for Fentanyl were generally stable over the course of the study, with mean and median concentrations similar at all time points. Two subjects showed high early fentanyl levels at 2.4 and 5.7 hours, respectively. However, this seem related to the number of times the subjects used the SSEC system: Subject 2002 (concentration peak at 2.4 hours, magenta line) used the SSEC 8 times in the first 3 hours after SSEC placement, and then not again for the next 8 hours; Subject 2009 (concentration peak at 5.7 hours, yellow line) used the SSEC 70 times during the 24 hours of SSEC placement, most frequently in the first 6 hours following SSEC placement. The number and type of AEs reported by these two subjects doesn't differ from the rest of the group. No SAEs were reported.

It was noted that the Inter-subject variability in concentrations was quite high. The company justifies this variability with the different individual titration of doses by each subject. This justification seems reasonable and acceptable. However, intra-subject variability for Fentanyl concentrations was low and tended to be stable within individual subjects.

For the measurement of 'Pain Intensity Score Over Time' the NRS score remained ≤4 until 60 hours post-application The Company states that 'interpretation of scores showing continued control of pain on treatment at this and later time points are confounded by the fact that there were 4 or fewer subjects still using SSEC systems'. This is acceptable.

The perception of success' of the SSEC as a method of pain control varies between patients ('good' or 'excellent' reported by 44 (72.1%) subjects at 24 hours, and by 46 (75.4%) subjects at the end of treatment) , parent/guardians ('good' or 'excellent' reported by 51 (83.6%) at 24 hours, and by 53 (86.9%) at the end of treatment and Investigators ('good' or 'excellent' was reported for 58 (95.1%) subjects at 24 hours, and for 60 (98.4%) subjects at the end of treatment). However, the overall feeling of success is high.

At least one rescue medication was received by 29 (47.5%) subjects during the treatment. Opioids were the most common rescue medication, used by 28 (45.9%) subjects. The most common opioid rescue medications used were hydromorphone in 19 (31.1%) subjects and oxycodone in 16 (26.2) subjects. Other rescue medications were used by fewer than 10% of subjects each.

A total of 21 (34.4%) subjects had 1 SSEC application, 34 (55.7%) subjects had 2 SSEC applications, and 6 (9.8%) subjects had 3 applications. The mean number of on-demand doses delivered from the 107 SSECs was 23.9, and the mean number of on-demand doses delivered per subject was 41.9

Mean duration of fentanyl exposure (i.e., duration of application of the device to the skin) was 36.1 hours.

Overall, it appears that the SSEC system is easy to use in this age group of the population and has been considered excellent or good by 75.4% of the subjects by the end of treatment.

The adherence of the system showed to be very good during the assessment period, with 90.7% SSEC systems remained adhered to ≥90% of the area.

Safety results

Safety Endpoints

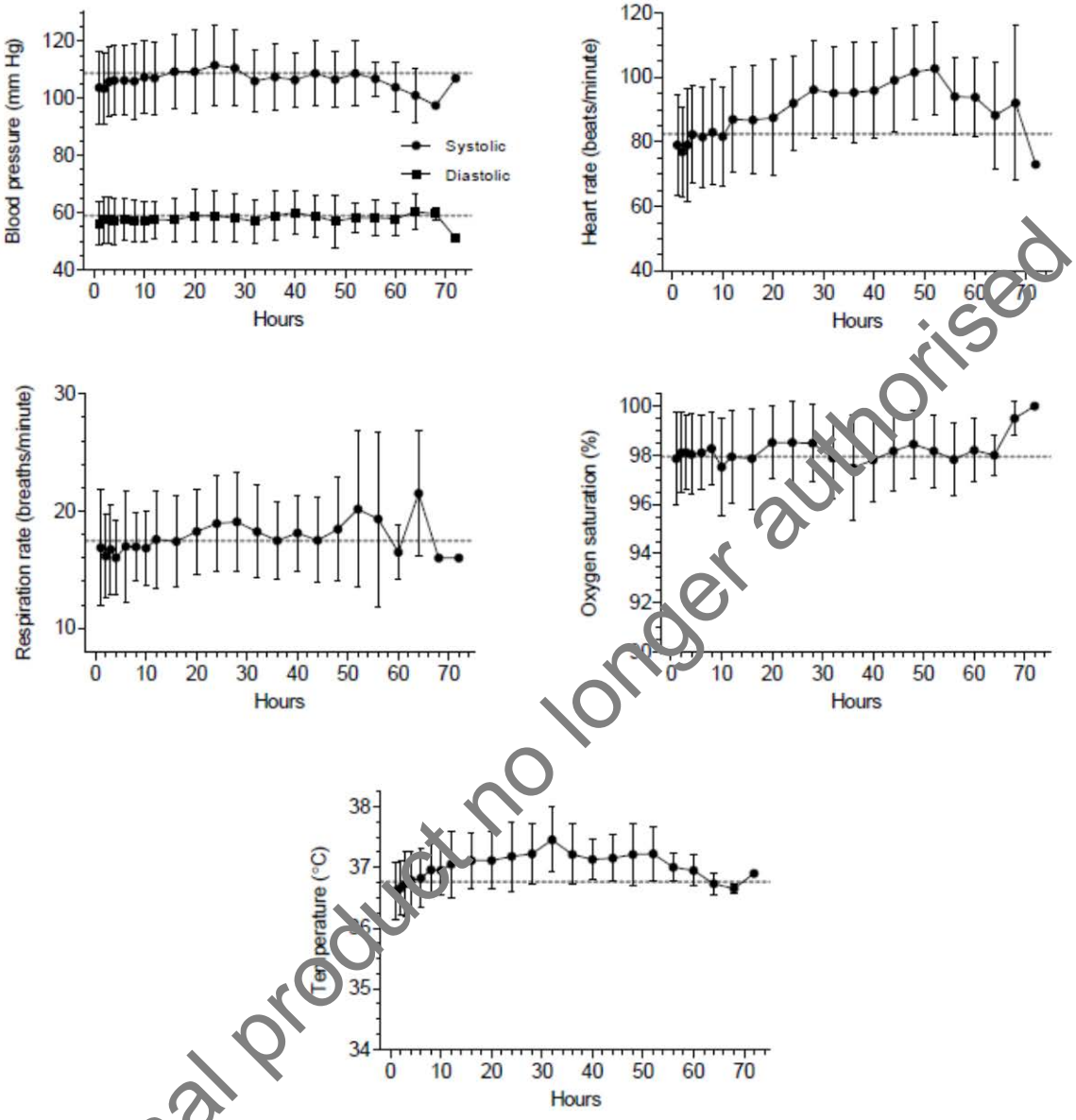
Endpoints for safety analyses included:

- Changes in vital signs from baseline, including CRRD
- Changes in the skin irritation score from baseline
- Incidence of adverse events(AEs)and SAEs

Changes in vital signs from baseline, including CRRD

No clinically meaningful changes in vital sign mean measurements (systolic and diastolic blood pressure, heart rate, temperature, respiration rate, O2 saturation) were observed. No TEAEs of bradypnea (and therefore, no cases of CRRD) were reported.

Figure 10: Vital Signs – Safety Population



Source: Table 14.3.4.1.

Note: Baseline was defined as the Day 1 sample collected pre-operatively, and is denoted by a dashed line.

CHMP comment

The individual vital signs data did not show any important changes during and at the end of the assessment period.

Changes in the skin irritation score from baseline

The median change from baseline in the skin irritation score for the first system applied was 1.0 point at 1 hour after SSEC removal, and 1.5 points at 24 hours after SSEC removal. For the second and third system applied, the median change from baseline at 1 and 24 hours after SSEC removal was 1.0 point. As the median scores at baseline were zero for each system, the median change at each timepoint also represents the median score.

Table 23: Skin Irritation Score – Safety Population

Skin Irritation Score, n (%)	SSEC Fentanyl 40 µg		
	Baseline	1 hour After SSEC Removal	24 hours After SSEC Removal
System 1 (N = 61)			
N	61	61	48
Mean (SD) change from baseline		1.1 (0.94)	1.8 (1.43)
Median change from baseline		1.0	1.5
Minimum, maximum change from baseline		0.0, 3.0	0.0, 6.0
0 No evidence of irritation	61 (100.0)	13 (21.3)	5 (8.2)
1 Minimal erythema, barely perceptible	0	31 (50.8)	19 (31.1)
2 Definite erythema, readily visible; minimal edema or minimal papular response	0	16 (26.2)	13 (21.3)
3 Erythema and papules	0	0	7 (11.5)
4 Definite edema	0	0	1 (1.6)
5 Erythema, edema, and papules	0	0	0
6 Vesicular eruption	0	1 (1.6)	3 (4.9)
7 Strong reaction spreading beyond the application site	0	0	0
8 Not assessed	0	0	13 (21.3)
System 2 (N = 40)			
N	39	39	34
Mean (SD) change from baseline		1.0 (0.61)	1.6 (1.33)
Median change from baseline		1.0	1.0
Minimum, maximum change from baseline		0.0, 2.0	0.0, 6.0

Skin Irritation Score, n (%)	SSEC Fentanyl 40 µg		
	Baseline	1 hour After SSEC Removal	24 hours After SSEC Removal
0 No evidence of irritation	39 (97.5)	7 (17.5)	4 (10.0)
1 Minimal erythema, barely perceptible	0	25 (62.5)	17 (42.5)
2 Definite erythema, readily visible; minimal edema or minimal papular response	0	7 (17.5)	8 (20.0)
3 Erythema and papules	0	0	2 (5.0)
4 Definite edema	0	0	1 (2.5)
5 Erythema, edema, and papules	0	0	1 (2.5)
6 Vesicular eruption	0	0	1 (2.5)
7 Strong reaction spreading beyond the application site	0	0	0
8 Not assessed	1 (2.5)	1 (2.5)	6 (15.0)
System 3 (N = 6)			
N	6	5	4
Mean (SD) change from baseline		1.0 (1.22)	0.8 (1.26)
Median change from baseline		1.0	1.0
Minimum, maximum change from baseline		-1.0, 2.0	-1.0, 2.0
0 No evidence of irritation	5 (83.3)	1 (16.7)	1 (16.7)
1 Minimal erythema, barely perceptible	1 (16.7)	2 (33.3)	2 (33.3)
2 Definite erythema, readily visible; minimal edema or minimal papular response	0	2 (33.3)	1 (16.7)
3 Erythema and papules	0	0	0
4 Definite edema	0	0	0
5 Erythema, edema, and papules	0	0	0
6 Vesicular eruption	0	0	0
7 Strong reaction spreading beyond the application site	0	0	0
8 Not assessed	0	1 (16.7)	2 (33.3)

Source: Table 14.3.3.4, Table 14.3.3.5.

Note: Statistical percentages are calculated using N at each timepoint. Baseline is defined as the assessment immediately before SSEC application.

Skin irritation score category totals are not reported as change from baseline, but as reported scores.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SD = standard deviation of the mean; SSEC = separated system with enhanced controller.

Application site erythema and application site papules occurred in 10 (16.4%) subjects each, with other application site reactions occurring in <5% of subjects. Nearly all application site reactions were mild in severity; 2 events each of application site erythema and application site papules were reported as moderate; and 2 events (1 event each of application site exfoliation, and application site reaction) were reported as severe. No applications site reactions were serious. One event of application site pruritus, mild in intensity, and considered definitely related to treatment, led to discontinuation of treatment.

Table 24: Incidence of Application Site Reactions by Preferred Term, in Descending Frequency – Safety Population

Preferred Term	SSEC Fentanyl 40 µg (N = 61) n (%)
Subject with any application site reaction	16 (26.2)
Application site erythema	10 (16.4)
Application site papules	10 (16.4)
Application site oedema	3 (4.9)
Application site discolouration	2 (3.3)
Application site exfoliation	2 (3.3)
Application site pruritus	2 (3.3)
Application site discomfort	1 (1.6)
Application site irritation	1 (1.6)
Application site reaction	1 (1.6)
Application site vesicles	1 (1.6)
Infusion site extravasation	1 (1.6)

Source: Table 14.3.3.1.

Note: Adverse events are coded using MedDRA, version 18.0.
Subjects with multiple events are only counted once within each MedDRA level.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller.

CHMP comment

Application site erythema and application site papules occurred in 10 (16.4%) subjects each, with other application site reactions occurring in <5% of subjects. Nearly all application site reactions were mild in severity, and none were serious. One event of application site pruritus, mild in intensity, and considered related to treatment led to discontinuation of treatment.

The median change from baseline in the skin irritation score was 1.0–1.5 points. The Applicant states that this is consistent with previous studies of IONSYS.

Incidence of adverse events(AEs)and SAEs

A total of 44 (72.1%) subjects reported a TEAE. Treatment-related (as assessed by the investigator) TEAEs were reported by 35 (57.4%) subjects. Only 1 (1.6%) subject reported a serious TEAE, which was not treatment-related. Treatment-emergent adverse events leading to discontinuation of treatment were reported in 2 (3.3%) subjects. There were no deaths on study.

Table 16: Summary of Subjects with Treatment-Emergent Adverse Events – Safety Population

Treatment-Emergent Adverse Event (TEAE) Category	SSEC Fentanyl 40 µg (N = 61) n (%)
At least 1 TEAE	44 (72.1)
At least 1 Related TEAE	35 (57.4)
At least 1 Serious TEAE	1 (1.6)
At least 1 Related, Serious TEAE	0
Any TEAE leading to discontinuation of treatment	2 (3.3)
Any TEAE leading to death	0

Source: Table 14.3.1.1.

Note: TEAEs are defined as those adverse events which were newly occurring or worsening after the first study drug intake. Adverse events are coded using MedDRA, version 18.0.

Related TEAEs are AEs related to study drug.

Abbreviations: N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; TEAE = treatment-emergent adverse event.

Treatment-Emergent Adverse Events

The system-organ class (SOC) with the highest incidence of TEAEs reported was Gastrointestinal disorders, which occurred in 29 (47.5%) subjects. The most frequent preferred terms (PTs) also occurred in this SOC: vomiting in 19 (31.1%) subjects, nausea in 18 (29.5%) subjects, and constipation in 11 (18.0%) subjects. Application site erythema and application site papules occurred in 10 (16.4%) subjects each, with other application site reactions occurring in <10% of subjects.

Table 17: Incidence of Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term, in Descending Frequency – Safety Population

System Organ Class, Preferred Term	SSEC Fentanyl 40 µg (N = 61) n (%)
Subject with any TEAE	44 (72.1)
Gastrointestinal disorders	29 (47.5)
Vomiting	19 (31.1)
Nausea	18 (29.5)
Constipation	11 (18.0)
General disorders and administration site conditions	21 (34.4)
Application site erythema	10 (16.4)
Application site papules	10 (16.4)
Pyrexia	7 (11.5)
Nervous system disorders	11 (18.0)
Dizziness	7 (11.5)
Skin and subcutaneous tissue disorders	11 (18.0)
Pruritus generalised	5 (8.2)
Respiratory, thoracic and mediastinal disorders	6 (9.8)
Atelectasis	4 (6.6)

Source: Table 14.3.1.2.1.

Note: TEAEs are defined as those adverse events which were newly occurring or worsening after the first study drug intake.
Adverse events are coded using MedDRA, version 18.0
Subjects with multiple TEAEs are only counted once within each MedDRA level.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; TEAE = treatment-emergent adverse event.

Opioid-Related Treatment-Emergent Adverse Events

The most common SOC with opioid-related TEAEs was Gastrointestinal disorders which occurred in 28 (45.9%) subjects.

The most common opioid-related TEAEs were vomiting occurring in 19 (31.1%) subjects, nausea in 18 (29.5%) subjects, and constipation in 11 (18.0%) subjects.

Table 18: Incidence of Opioid-Related Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term, in Descending Frequency – Safety Population

System Organ Class, Preferred Term	SSEC Fentanyl 40 µg (N = 61) n (%)
Subject with any opioid-related TEAE	31 (50.8)
Gastrointestinal disorders	28 (45.9)
Vomiting	19 (31.1)
Nausea	18 (29.5)
Constipation	11 (18.0)

Source: Table 14.3.1.2.4.

Note: TEAEs are defined as those adverse events which were newly occurring or worsening after the first study drug intake.
Adverse events are coded using MedDRA, version 18.0.
Subjects with multiple TEAEs are only counted once within each MedDRA level.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; TEAE = treatment-emergent adverse event.

Treatment-Emergent Adverse Events by Severity

Most TEAEs were mild or moderate in severity occurring in 25 (41.0%) and 16 (26.2%) subjects, respectively; with severe events occurring in only 3 (4.9%) subjects.

Severe TEAEs were nausea, application site exfoliation, and application site reaction (each occurring in 1 [1.6%] subject).

Table 19: Incidence of Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term, in Descending Frequency, by Maximum Severity – Safety Population

System Organ Class, Preferred Term, Severity	SSEC Fentanyl 40 µg (N = 61) n (%)
Subject with any TEAE	
Mild	25 (41.0)
Moderate	16 (26.2)
Severe	3 (4.9)

System Organ Class, Preferred Term, Severity	SSEC Fentanyl 40 µg (N = 61) n (%)
Gastrointestinal disorders	
Mild	20 (32.8)
Moderate	8 (13.1)
Severe	1 (1.6)
Vomiting	
Mild	14 (23.0)
Moderate	5 (8.2)
Severe	0
Nausea	
Mild	13 (21.3)
Moderate	4 (6.6)
Severe	1 (1.6)
Constipation	
Mild	8 (13.1)
Moderate	3 (4.9)
Severe	0
General disorders and administration site conditions	
Mild	17 (27.9)
Moderate	2 (3.3)
Severe	2 (3.3)
Application site erythema	
Mild	8 (13.1)
Moderate	2 (3.3)
Severe	0
Application site pa[illegible]	
Mild	8 (13.1)
Moderate	2 (3.3)
Severe	0
Pyrexia	
Mild	7 (11.5)
Moderate	0
Severe	0

System Organ Class, Preferred Term, Severity	SSEC Fentanyl 40 µg (N = 61) n (%)
Nervous system disorders	
Mild	9 (14.8)
Moderate	2 (3.3)
Severe	0
Dizziness	
Mild	6 (9.8)
Moderate	1 (1.6)
Severe	0
Skin and subcutaneous tissue disorders	
Mild	7 (11.5)
Moderate	4 (6.6)
Severe	0
Pruritus generalised	
Mild	5 (8.2)
Moderate	0
Severe	0
Respiratory, thoracic and mediastinal disorders	
Mild	5 (8.2)
Moderate	1 (1.6)
Severe	0
Atelectasis	
Mild	3 (4.9)
Moderate	1 (1.6)
Severe	0

Source: Table 14.3.1.4.1.

Note: TEAEs are defined as those adverse events which were newly occurring or worsening after the first study drug intake.
Adverse events are coded using MedDRA, version 18.0.
Subjects with multiple TEAEs are only counted once within each MedDRA level at the greatest severity.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; TEAE = treatment-emergent adverse event.

Opioid-Related Treatment-Emergent Adverse Events by Severity

Most opioid-related TEAEs were mild or moderate in severity occurring in 21 (34.4%) and 9 (14.8%) subjects, respectively; with a severe event of nausea occurring in only 1 (1.6%) subject.

Drug-Related Treatment-Emergent Adverse Events

The most common SOCs with drug-related TEAEs were Gastrointestinal disorders which occurred in 27 (44.3%) subjects, General disorders and administration site conditions in 14 (23.0%) subjects, and Skin and subcutaneous tissue disorders in 8 (13.1%) subjects.

The most common drug-related TEAEs were nausea occurring in 18 (29.5%) subjects; vomiting in 11 (18.0%) subjects; and constipation, application site erythema, and application site papules in 10 (16.4%) of subjects each.

Table 20: Incidence of Drug-Related Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term, in Descending Frequency – Safety Population

System Organ Class, Preferred Term	SSEC Fentanyl 40 µg (N = 61) n (%)
Subject with any related TEAE	35 (57.4)
Gastrointestinal disorders	27 (44.3)
Nausea	18 (29.5)
Vomiting	11 (18.0)
Constipation	10 (16.4)
General disorders and administration site conditions	14 (23.0)
Application site erythema	10 (16.4)
Application site papules	10 (16.4)
Skin and subcutaneous tissue disorders	8 (13.1)
Pruritus generalised	4 (6.6)

Source: Table 14.3.1.2.3.

Note: TEAEs are defined as those adverse events which were newly occurring or worsening after the first study drug intake.
Adverse events are coded using MedDRA, version 18.0.
Subjects with multiple TEAEs are only counted once within each MedDRA level, with the most related category presented.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; TEAE = treatment-emergent adverse event.

Deaths

No deaths occurred on study.

Other Significant Adverse Events

Serious Treatment-Emergent Adverse Events

Only 1 serious TEAE of atelectasis occurred in 1 (1.6%) subject. It concerns a 16-year-old female patient who underwent spinal fusion.

After surgery, she was treated with IONSYS SSEC during two days for the management of acute postoperative pain and received a total of 40 doses. Medical history was positive for scoliosis, muscle spasm, and an undescribed infection. Concomitant medications

included ceftriaxone, and post-treatment medications (i.e., post-IONSYS SSEC) included oral oxycodone.

One week after the first treatment with Ionsys, the subject experienced a squeezing sensation in her heart, palpitations and shortness of breath. She was treated with cefepime and vancomycin for suspected nosocomial pneumonia. A complete blood count and blood work-up were not consistent with infection. A blood culture from an outside hospital showed no growth. Additional tests, including electrocardiogram, metabolic panel, troponin and d-dimer were unremarkable. Chest X-ray showed patchy airspace disease in the left lower lobe, raising concerns of atelectasis versus pneumonia. Throughout the hospitalization, she did not show signs of respiratory distress and continued to be afebrile and without cough. A final diagnosis of atelectasis was entertained.

The subject was encouraged to use incentive spirometer along with adequate pain control and three days after the event, the subject recovered.

The investigator considered the event of atelectasis as moderate and unlikely related to the study drug. The most likely cause of the event was pain-related shallow breathing following surgery.

Treatment-Emergent Adverse Events Leading to Discontinuation of Treatment

A TEAE of application site pruritus, mild in intensity, and considered definitely related to treatment; and a TEAE of lethargy, moderate in intensity, and considered definitely related to treatment occurred in 1 (1.6%) subject each.

Table 22: Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation of Treatment – Safety Population

System Organ Class, Preferred Term	SSEC Fentanyl 40 µg (N = 61) n (%)
Subject with any TEAE leading to discontinuation of treatment	2 (3.3)
General disorders and administration site conditions	1 (1.6)
Application site pruritus	1 (1.6)
Nervous system disorders	1 (1.6)
Lethargy	1 (1.6)

Source: Table 14.3.1.1, Listing 16.2.14.

Note: TEAEs are defined as those adverse events which were newly occurring or worsening after the first study drug intake.
Adverse events are coded using MedDRA, version 18.0.
Subjects with multiple TEAEs are only counted once within each MedDRA level.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the specified group; n = number of subjects in the category; SSEC = separated system with enhanced controller; TEAE = treatment-emergent adverse event.

CHMP comment

There were no deaths or other AEs resulted in death.

TEAEs were reported by 44 (72.1%) subjects.

One serious TEAE of atelectasis occurred in 1 (1.6%) subject.
Treatment-emergent adverse events leading to discontinuation of treatment were reported in 2 (3.3%) subjects (application site pruritus and lethargy, both considered related to study drug).
The most frequent TEAEs were common opioid side-effects: vomiting in 19 (31.1%) subjects, nausea in 18 (29.5%) subjects, and constipation in 11 (18.0%) subjects. Only 1 (1.6%) subject reported a serious TEAE (atelectasis), which was considered not treatment-related.
Application site erythema and application site papules occurred in 10 (16.4%) subjects.
Other application site reactions occurring in <5% of subjects. However, most of the application site reactions were mild in severity, and none were serious.
One event of application site pruritus led to discontinuation of treatment, although considered mild in intensity but related to treatment.
The median change from baseline in the skin irritation score was -0.5 to -1.5 points, which is consistent with previous studies of IONSYS.

No clinically meaningful changes in vital sign mean measurements (systolic and diastolic blood pressure, heart rate, temperature, respiration rate, O_2 saturation) were observed. No TEAEs of bradypnea (and therefore, no cases of CRRD) were reported.

Conclusions:

Overall, the number, type and incidence of adverse events are in line with the already known safety profile of Ionsys. No new AEs or concerns have emerged that require further investigations.

Discussion on clinical aspects

Fentanyl is an opioid that has been administered parenterally as an anaesthetic and analgesic for more than 40 years. Fentanyl solutions for injections are already approved for opioid naïve children and adolescents going for short surgical procedures.

The results of study PD2013-002 are submitted as per Article 46 of Regulation (EC) No 1901/2006. In line with the European Medicines Agency (EMA) post-authorisation procedural advice for users of the centralised procedure, this Article 46 paediatric study submission is submitted as a post-approval measure. This study is part of the IONSYS® Paediatric Investigation Plan (PIP) EMEA-001509-PIP01-13-M01, study number 1369672683823 (EudraCT: 2014-002405-37).

The objective of the PD2013-002 study was to evaluate the safety and clinical utility of the active SSEC fentanyl 40 µg for the management of acute postoperative pain in paediatric subjects from 12 to less than 18 years of age.

The MAH stated that, based on the results of this study and in accordance with Article 16(2) of Regulation (EC) No 726/2004, the MAH states that the data submitted do not influence the benefit risk balance for IONSYS® and plans to update the IONSYS® European Union (EU) summary of product characteristics (SmPC) to include information about the adolescent population in the first quarter of 2018.

The number, type and incidence of adverse events recorded during the study are in line with the already known safety profile of Ionsys. No new AEs or concerns have emerged that require further investigations.

Overall, it appears that the SSEC system is easy to use in the 12-18 years old age group and has been considered excellent or good by 75.4% of the subjects by the end of treatment.

The adherence of the system showed to be very good during the assessment period, with 90.7% SSEC systems remained adhered to ≥90% of the area.

3. CHMP overall conclusion and recommendation

The primary aim of the study was to evaluate the safety and clinical utility of the active SSEC fentanyl 40 µg for the management of acute postoperative pain in paediatric subjects from 12 to less than 18 years of age.

No new AEs or concerns have emerged that require further investigations. The results of the study show that the SSEC system is easy to use in the 12-18 years old age group. The following clarifications are requested.

4. Additional clarification requested

1. The Applicant should clarify if, with the data presented, and the well-known pharmacological profile of Fentanyl in adults and the paediatric population, they are planning to apply for an indication for this age group which would require submission of a type 2 variation.
2. The applicant should provide a short overview of the clinical data available in the adolescent population for studies previously conducted.

MAH responses to Request for supplementary information

The Applicant should clarify if, with the data presented, and the well-known pharmacological profile of Fentanyl in adults and the paediatric population, they are planning to apply for an indication for this age group which would require submission of a type 2 variation.

MAH response

The MAH has ceased the marketing of IONSYS as of 01 September 2017 and it is no longer being distributed or in use. Therefore the MAH does not plan to apply for an indication for adolescents.

CHMP's response

The MAH's response with regards to the lack of intention to apply for an adolescent indication is noted. The study assessed is part of an agreed PIP (EMEA-001509-PIP01-13-M01) which consists of a number of agreed paediatric measures (including further paediatric clinical studies) in support of the indication: "management of acute moderate to severe post-operative pain for use in children 2 to less than 18 years of age in a hospital setting". The PIP is due to be completed by February 2022 and the MAH of IONSYS is reminded of the legal obligation to fully complete all the deferred measures or otherwise liaise with EMA/PDCO.

The applicant should provide a short overview of the clinical data available in the adolescent population for studies previously conducted.

MAH response

As described in the addendum to the clinical overview, the clinical development for IONSYS included 3 paediatric studies (C-2000-005, C-2001-006, and C-96-057) using two prior versions of IONSYS®: E-TRANS System (ETS) 25 µg and/or the ETS 40 µg system. Two of those studies conducted between 2000 and 2002 included adolescent paediatric subjects: study C-2000-005-02 (An open evaluation of Safety and Clinical Utility of ETRANS (fentanyl) for Management of Post-Operative Pain in Children and Adolescents) and study C-2001-006-02 (Pharmacokinetic Study of E-TRANS (fentanyl hydrochloride) System 25 µg and 40 µg in Pediatric Intraoperative Patients). Study C-2001-006-02 was conducted in children aged 6 to less than 18 years of age who were stratified by age into one of three groups: Group I (6 – 8 years), Group II (9 –12 years), or Group III (13 – 17 years). Study C-2000-005-02 was conducted in children aged 6 to less than 16 years of age who were stratified by body weight into one of three groups: Group I (20.0 to 29.9 kg), Group II (30.0 to 39.9 kg), or Group III (≥40.0 kg).

The results for the 13 to 17 years old age group only are provided for C-2001-006-02. For study C-2000-005-02, since results were analysed by weight groups only, data presented are for paediatric patients with a weight ≥ 40 kg which was of equivalent weight to the subjects included in study PD2013-002.

Study C-2000-005-02

This study was an open label multicentre study of efficacy and safety in which paediatric patients received IONSYS ETS (25 µg/dose or 40 µg/dose) for up to three consecutive days post-operatively. This study was conducted in children aged 6 to less than 16 years of age who were stratified by body weight into one of three groups: Group I (20.0 to 29.9 kg), Group II (30.0 to 39.9 kg), or Group III (≥40.0 kg). A total of 121 subjects were treated in the study, of those, 48 (39.7%) were in the ≥40 kg group which was of equivalent weight to the subjects included in study PD2013-002. All subjects initiated treatment with IONSYS ETS 25 µg and were allowed supplemental medication (IV fentanyl) during the first three hours of treatment. If a subject was having inadequate analgesia three hours after the system was first applied, the 25 µg system could be removed and replaced with a 40 µg system for the remainder of that 24 hour treatment period.

The majority of subjects who increased to the 40 µg system were in the ≥40 kg group (21 of 28 subjects; 75%). The results provided below are for the ≥40 kg group only.

Efficacy Results

The ≥ 40 kg subjects rated IONSYS ETS as a good or excellent method of pain control at the end of the first 24-hour treatment period (77.1%) and at the last assessment on study (81.3%). Investigators rated the IONSYS ETS as a good or excellent method of pain control for 89.6% of ≥ 40 kg subjects at the end of the first 24–hour treatment period and for 93.8% of subjects at the last investigator global assessment.

Safety Results

Adverse events

The most frequently reported AEs in ≥ 40 kg subjects were common opioid (nausea [39.6%], vomiting [22.9%]) and postoperative (fever [37.5%]) side effects (see Table 1). The most common AEs were nausea, vomiting, pruritus (18.8%), and ASR vesicles (16.7%). ASR reported were mild or moderate and resolved spontaneously upon removal of the IONSYS ETS system.

Table 1: All Adverse Events with Incidence of ≥5% In any Weight Group (All Treated Patients)

Number (%) of patients who reported adverse events[a]	Weight Group (kg) 20.0-29.9 kg (n=38)	30.0-39.9 kg (n=35)	≥40 kg (n=48)	Total (n=121)
Nausea	13 (34.2%)	15 (42.9%)	19 (39.6%)	47 (38.8%)
Vomiting	18 (47.4%)	18(51.4%)	11 (22.9%)	47 (38.8%)
Fever	10 (26.3%)	12 (34.3%)	18 (37.5%)	40 (33.1%)
Pruritus	7 (18.4%)	8 (22.9%)	9 (18.8%)	24 (19.8%)
Application site reaction-Vesicles	4 (10.5%)	7 (20.0%)	8 (16.7%)	19 (15.7%)
Hypertonia	1 (2.6%)	4(11.4%)	7 (14.6%)	12 (9.9%)
Headache	3 (7.9%)	2 (5.7%)	6 (12.5%)	11(9.1%)
Tachycardia	3 (7.9%)	4(11.4%)	2 (4.2%)	9 (7.4%)
Hypoxia	2 (5.3%)	2 (5.7%)	5 (10.4%)	9 (7.4%)
Dizziness	2 (5.3%)	3 (8.6%)	3 (6.3%)	8 (6.6%)
Application site reaction-Itching	1 (2.6%)	1 (2.9%)	3 (6.3%)	5 (4.1%)
Anxiety	0	2 (5.7%)	2 (4.2%)	4 (3.3%)
Urticaria	0	1 (2.9%)	3 (6.3%)	4 (3.3%)

Number (%) of patients who reported adverse events[a]	Weight Group (kg) 20.0-29.9 kg (n=38)	30.0-39.9 kg (n=35)	≥40 kg (n=48)	Total (n=121)
Anemia	2 (5.3%)	0	1 (2.1%)	3 (2.5%)
Application site reaction-Other	2 (5.3%)	0	1 (2.1%)	3 (2.5%)
Rash	2 (5.3%)	0	1 (2.1%)	3 (2.5%)
Vasodilatation	2 (5.3%)	0	0	2 (1.7%)

[a] A patient may be reported in more than one COSTART category.
Source: Clinical Study Report for study C-2000-005-02, Table M

The overall incidence of AEs for ≥ 40 kg group appears in Table 2.

Table 2: Overall Incidence of Adverse Events (Percentage of Patients) by Maximum Severity and Relationship to Treatment

≥ 40kg group (n=48)	MILD	MODERATE	SEVERE
Related	54.2%	35.4%	0
Not Related	43.8%	25.0%	8.3%

Source: Clinical Study Report for study C-2000-005-02, Table N

Treatment-related adverse events

No treatment related severe adverse events were reported in the ≥ 40 kg group. Thirty-four (34) of the 48 treated patients (70.8%) in that group experienced at least one adverse event that was judged as probably or possibly related to study treatment. The most common

treatment-related adverse events were nausea and vomiting (39.6% and 20.8%, respectively), which are associated with opioid analgesics (Table 11.3.1.1-4 from Clinical Study Report for study C-2000-005-02). Other common treatment-related adverse events included erythema at 24 hour post-system removal assessment and other ASRs. Erythema resolved, on average, within 3 weeks without treatment.

SAEs

No patient in the ≥ 40 kg group died and there were no reported events of clinically relevant respiratory depression (CRRD). Five patients in the ≥ 40 kg group experienced SAEs (Table O from Clinical Study Report for study C-2000-005-02). None of the SAEs were considered related to study treatment.

Conclusions

The IONSYS ETS 25 µg system and 40 µg system were both successfully used for patient controlled analgesia in this paediatric population (≥ 40 kg group) and were well tolerated. Overall, both patients and investigators rated IONSYS ETS treatment favourably. Patients rated IONSYS ETS a good or excellent method of pain control at the last assessment on study (81.3 %). Investigators rated the IONSYS ETS systems as easy for all patients to use and suitable for the patient population. In addition, pain intensity scores decreased for all patients in the study. Safety analyses showed a safety profile similar to fentanyl use in adults. The AEs generally reflected the subject's postoperative status and the administration of opioid analgesics. The most common treatment-related adverse events were nausea and vomiting (39.6% and 20.8%, respectively), which are associated with opioid analgesics. Other common treatment-related adverse events included erythema at 24 hours post system removal assessment and other ASRs. Erythema resolved, on average, within 3 weeks without treatment. No patients died on study and no patient experienced clinically relevant respiratory depression. For the 5 patients who reported SAEs, none of the events were stated to be related to study treatment.

Study C-2001-006-02

The primary purpose of this study was to evaluate the pharmacokinetics of fentanyl in paediatric patients following four sequential doses of fentanyl from the IONSYS ETS 25 and 40 µg systems during surgery for paediatric patients aged 6 – 17 years. In this study, a total of 25 patients undergoing surgery were enrolled; they were stratified by age into one of three groups: Group I (6 – 8 years), Group II (9 –12 years), or Group III (13 – 17 years). The results presented below are for Group III (13 – 17 years) only.

Pharmacokinetic Results

In this study, a total of 25 patients were enrolled, and data from all 25 patients were used in the non-compartmental pharmacokinetic (PK) analysis. Of the 25 enrolled, 9 were aged 13 through 17 years. The results for these children are outlined in Table 3. Following four sequential 10-minute doses of IONSYS ETS 40 µg administered to children 13-17 years old during surgery, the mean maximum serum concentration (Cmax) was 0.23 ng/mL. The mean time to reach the maximum serum concentration (Tmax) was 0.71 hours. The mean terminal half-life (t1/2) was 3.13 hours. The mean AUCinf value was 0.99 ng.h\mL. Inter-subject variability in AUC values was high.

Table 3: Mean ± SD (n) Serum Fentanyl Pharmacokinetic Parameter Values following IONSYS ETS Treatments (Four 40 µg doses)

Parameters	Adolescents (13-17 years) n=9
C_{max}	0.23 ±0.22[a] (n=9)
T_{max}	0.71 ±0.22[a] (n=7)
$T_{1\backslash 2}$ (h)	3.13 ±2.21 (n=6)
k (h^{-1})	0.41 ±0.36 (n=6)
AUC_{inf}	0.99 ±0.95 (n=7)

Source: Table F in final report for protocol C-2001-006-02

[a] Two patients (110 and 111) with no quantifiable concentrations were included in the mean estimate for C_{max} and were excluded from the mean estimate of T_{max}.

Safety Results

No serious adverse events (SAEs) were reported during this study. All adverse events (AEs) were of mild or moderate severity. The only AE reported by more than one adolescent patient was nausea (n=2, 22.2%) (Table 11.1.3-1 from C-2001-006-02 report). No adolescent patients had application site reaction (ASR) at the application sites. No new safety issues were identified with the IONSYS ETS 40 µg system studied in this adolescent paediatric population.

Overall Conclusion for Study C-2001-006-02

The pharmacokinetics of fentanyl were studied in 25 paediatric patients (6-17 years) undergoing surgery. Of the 25 enrolled, 9 were aged 13 through 17 years and received IONSYS ETS 40 µg/dose. Variability in AUC in this age group is similar to that observed in healthy adult volunteers receiving six sequential 40 µg doses of IONSYS ETS (C-2001-009). No SAEs were reported during this study. All AEs were of mild or moderate severity. The only AE reported by more than one adolescent patient was nausea (n=2, 22.2%); no adolescent patients had ASR at the application sites. No new safety issues were identified with the IONSYS ETS 40 µg systems studied in this adolescent paediatric population.

Overall Conclusions

The results from these 2 studies in the adolescents' sub-groups showed IONSYS ETS to be effective and well-tolerated. Safety analyses showed a safety profile similar to IONSYS use in adults, with no reports of serious opioid-related AEs. No new safety issues were identified with the IONSYS ETS studied in this paediatric population. Results were consistent with earlier adult and subsequent adult and paediatric studies of IONSYS, including the recently completed paediatric adolescent study PD2013-002.

CHMP's assessment of the response

The Applicant has provided a short overview of the clinical studies conducted in adolescents available as requested by the CHMP.

The discussion refers to 3 paediatric clinical studies (C-2000-005, C-2001-006 and C-96-057) using two prior versions of IONSYS®: ETS 25 µg and/or the ETS 40 µg system. Studies C-2000-005 and C-2001-006 included adolescents.

Studies C-2000-005 (121 patients) and study C-95-057 (3 patients) had a total of 124 paediatric postoperative subjects 5–16 years of age treated with the ETS fentanyl 25 µg/dose system. Children were stratified by body weight (Group I (20.0 to 29.9 kg), Group II (30.0 to 39.9 kg), or Group III (≥40.0 kg).

In study C-2000-005, subjects were initially treated with the 25 µg/dose systems with the option to be titrated up to 40 µg. Twenty-eight of the subjects were titrated to the 40 µg dose after experiencing inadequate analgesia with the 25 µg system. Of the 28 subjects who required the 40 µg dose, 21 (75%) subjects weighed more than 40 kg.

In study C-2001-006, twenty-five paediatric subjects were administered 4 sequential intraoperative doses from the 25 µg system (subjects 6–12 years of age) or the 40 µg system (13–17 years of age) that were conducted using a prior version of IONSYS®: ETS 25 µg and/or the ETS 40 µg system.

The overall conclusions of these studies are that the pharmacokinetics, efficacy and safety of fentanyl patches in adolescents are comparable to adults. The most common treatment-related adverse events were nausea and vomiting, which are associated with opioid analgesics. No unexpected AEs were recorded.

Although these studies were conducted with prior versions of the patches, and can only be used as supportive data, there are no safety or efficacy concerns emerging from this studies that can affect the conclusion of the original assessment report.

No additional clarifications are required.

☒ Fulfilled:

No regulatory action required.