



Clinical trial results:

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 Pediatric Patients 12 to Less Than 18 Years of Age

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-002405-37 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 12 September 2016 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 20 November 2018 |
| First version publication date | 14 July 2017 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Clarification of the timeframe for the primary end point (assessment of participant's ability to use the SSEC). |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | PD2013-002 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02395653 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Incline Therapeutics Inc., a wholly owned subsidiary of The Medicines Company |
| Sponsor organisation address | 900 Saginaw Drive, Suite 200, Redwood City, United States, 94063 |
| Public contact | Incline Therapeutics Inc., a wholly owned subsidiary of The Medicines Company, Global Health Science Center, +1 650-241-6800, medical.information@themedco.com |
| Scientific contact | Incline Therapeutics Inc., a wholly owned subsidiary of The Medicines Company, Global Health Science Center, +1 650-241-6800, medical.information@themedco.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001509-PIP01-13 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No | Yes |

| |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 June 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 September 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and clinical utility of the active, separated system with enhanced controller (SSEC) fentanyl 40 micrograms (mcg) for the management of acute, postoperative pain in pediatric participants, 12 to less than 18 years of age.

Protection of trial subjects:

This study was conducted under the supervision of medical personnel experienced with conducting studies of opioids in children, in accordance with International Conference on Harmonisation Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 29 June 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 71 |
| Worldwide total number of subjects | 71 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 71 |

| | |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Pediatric participants from 12 to less than 18 years of age who had undergone general or regional anesthesia for elective abdominal, pelvic/genitourinary, orthopedic, or thoracic surgery.

Pre-assignment

Screening details:

Screening was to take place within 3 weeks of the start of the study. Screening assessments included review of inclusion/exclusion criteria, signature of informed consent, medical history, height, weight, vital signs, and American Society of Anesthesiologists physical status. Participants were also instructed on the use of the SSEC.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | IONSYS (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------|
| Arm title | SSEC |
|-----------|------|

Arm description:

Post-surgery, participants received IONSYS, (fentanyl hydrochloride), an SSEC fentanyl transdermal system (hereafter referred to as SSEC), that provided on-demand systemic delivery of 40 mcg fentanyl per dose for up to 24 hours, or a maximum of 80 doses, whichever came first, for up to 3 consecutive days (up to 72 hours).

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | IONSYS (fentanyl hydrochloride) |
| Investigational medicinal product code | |
| Other name | SSEC fentanyl |
| Pharmaceutical forms | Transdermal system |
| Routes of administration | Transdermal use |

Dosage and administration details:

IONSYS® is a participant-controlled fentanyl transdermal system that provides on demand systemic delivery of 40 mcg fentanyl per dose for up to 24 hours, or a maximum of 80 doses, whichever comes first. The start of the treatment period (that is to say, Hour 0) began at the time the SSEC system was first assembled and applied to the participant's intact non-irritated skin on the chest or upper outer arm. As needed, the participant could continue to use 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 new location. Each on-demand dose delivered a nominal 40 mcg fentanyl dose over a 10-minute period, with a maximum of 6 doses delivered each hour.

| Number of subjects in period 1 | SSEC |
|---|------|
| Started | 71 |
| Received at least 1 dose of study drug | 61 |
| Completed | 59 |
| Not completed | 12 |
| Consent withdrawn by subject | 1 |
| Screen failure - exclusion criteria met | 4 |

| | |
|--|---|
| Participant had SSEC application but with 0 dose | 1 |
| Screen failure - Investigator decision | 1 |
| Screen failure - inclusion criteria not met | 3 |
| Screen failure-consent withdrawn by participant | 1 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | SSEC |
|-----------------------|------|

Reporting group description:

Post-surgery, participants received IONSYS, (fentanyl hydrochloride), an SSEC fentanyl transdermal system (hereafter referred to as SSEC), that provided on-demand systemic delivery of 40 mcg fentanyl per dose for up to 24 hours, or a maximum of 80 doses, whichever came first, for up to 3 consecutive days (up to 72 hours).

| Reporting group values | SSEC | Total | |
|---|--------|-------|--|
| Number of subjects | 71 | 71 | |
| Age categorical | | | |
| Participants aged 12 years to less than 18 years | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 71 | 71 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 14.7 | | |
| standard deviation | ± 1.51 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 50 | 50 | |
| Male | 21 | 21 | |

End points

End points reporting groups

| | |
|-----------------------|------|
| Reporting group title | SSEC |
|-----------------------|------|

Reporting group description:

Post-surgery, participants received IONSYS, (fentanyl hydrochloride), an SSEC fentanyl transdermal system (hereafter referred to as SSEC), that provided on-demand systemic delivery of 40 mcg fentanyl per dose for up to 24 hours, or a maximum of 80 doses, whichever came first, for up to 3 consecutive days (up to 72 hours).

| | |
|----------------------------|----------------------|
| Subject analysis set title | Evaluable Population |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The evaluable population consists of all participants who received fentanyl from the SSEC for at least 3 hours. The evaluable population was used for the primary analysis on clinical utility, pain intensity, and global assessments.

| | |
|----------------------------|-------------------|
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population consists of all participants who received at least 1 dose of fentanyl from the SSEC. The safety population was used for safety analysis.

Primary: Assessment Of Participant's Ability To Use The SSEC

| | |
|-----------------|--|
| End point title | Assessment Of Participant's Ability To Use The SSEC ^[1] |
|-----------------|--|

End point description:

Investigator's assessment of participant's ability to use the SSEC system safely and effectively. The assessment consisted of a 4-level categorical evaluation (poor, fair, good, and excellent).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Completed at the time of the participant's termination of study treatment (up to 72 hours after study drug administration).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Because of the descriptive nature of this study, no formal statistical hypothesis testing was performed.

| End point values | SSEC | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 61 | | | |
| Units: participants | | | | |
| Poor | 1 | | | |
| Fair | 2 | | | |
| Good | 10 | | | |
| Excellent | 48 | | | |
| Missing | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Assessment Of Adherence Of The SSEC System To Skin

| | |
|-----------------|---|
| End point title | Assessment Of Adherence Of The SSEC System To Skin ^[2] |
|-----------------|---|

End point description:

The adhesion of each SSEC 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. The number of SSEC systems for all time points in each category is presented.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Immediately prior to removal at each 24-hour time point, or at early withdrawal, for up to 3 consecutive days (up to 72 hours).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Because of the descriptive nature of this study, no formal statistical hypothesis testing was performed.

| End point values | SSEC | | | |
|--|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 61 ^[3] | | | |
| Units: SSEC systems | | | | |
| ≥90% of area with no edges unattached, N=107 | 97 | | | |
| 75% to 89%, N=107 | 6 | | | |
| <75% adhered and not taped, N=107 | 3 | | | |
| System was secured with tape, N=107 | 1 | | | |
| Not assessed, N=107 | 0 | | | |

Notes:

[3] - 107 SSEC systems used by 61 participants were evaluated for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline To 1 Hour And 24 Hours In Skin Irritation Score After SSEC Removal

| | |
|-----------------|---|
| End point title | Change From Baseline To 1 Hour And 24 Hours In Skin Irritation Score After SSEC Removal |
|-----------------|---|

End point description:

Skin irritation at the SSEC application site was to be assessed immediately prior to placement of the study system and at 1 and 24 hours after removal of each study system. The application site was to be scored using the following scale: 0=No evidence of irritation; 1=Minimal erythema, barely perceptible; 2=Definite erythema, readily visible, minimal oedma, or minimal papular response; 3=Erythema and papules; 4=Definite oedma; 5=Erythema, oedma, and papules; 6=Vesicular eruption; 7=Strong reaction spreading beyond the application site.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, 1 hour and 24 hours after SSEC removal.

| End point values | SSEC | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 61 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| System 1, Hour 1, N=61 | 1.1 (± 0.94) | | | |
| System 1, Hour 24, N=48 | 1.8 (± 1.43) | | | |
| System 2, Hour 1, N=39 | 1 (± 0.61) | | | |
| System 2, Hour 24, N=34 | 1.6 (± 1.33) | | | |
| System 3, Hour 1, N=5 | 1 (± 1.22) | | | |
| System 3, Hour 24, N=4 | 0.8 (± 1.26) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number Of Participants To Experience Clinically Relevant Respiratory Depression (CRRD)

| | |
|-----------------|--|
| End point title | Number Of Participants To Experience Clinically Relevant Respiratory Depression (CRRD) |
|-----------------|--|

End point description:

Respiratory function and occurrence of CRRD was defined as simultaneous occurrence of bradypnoea (respiratory rate <10 breaths per minute for participants 9-15 years of age and sustained for 1 minute, or <8 breaths per minute for participants 16-17 years of age), with excessive sedation (that is, the participant is not easily aroused).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the time of application of the first system through 7 days following end of study drug administration.

| End point values | SSEC | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 61 | | | |
| Units: Number of Participants | | | | |
| Bradypnoea | 0 | | | |
| Excessive Sedation | 0 | | | |
| Simultaneous Bradypnoea and Excessive Sedation | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of application of the first system through 7 days following the end of study drug administration.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | SSEC |
|-----------------------|------|

Reporting group description:

Post-surgery, participants received an SSEC fentanyl iontophoretic transdermal system that provided on-demand systemic delivery of 40 mcg fentanyl per dose for up to 24 hours, or a maximum of 80 doses, whichever came first, for up to 3 consecutive days (up to 72 hours).

| Serious adverse events | SSEC | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | SSEC | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 61 (72.13%) | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 61 (11.48%) | | |
| occurrences (all) | 9 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------------|--|--|
| Application site erythema subjects affected / exposed occurrences (all) | 10 / 61 (16.39%) 10 | | |
| Application site papules subjects affected / exposed occurrences (all) | 10 / 61 (16.39%) 10 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 7 / 61 (11.48%) 7 | | |
| Gastrointestinal disorders | | | |
| Vomiting subjects affected / exposed occurrences (all) | 19 / 61 (31.15%) 23 | | |
| Nausea subjects affected / exposed occurrences (all) | 18 / 61 (29.51%) 19 | | |
| Constipation subjects affected / exposed occurrences (all) | 11 / 61 (18.03%) 11 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus generalised subjects affected / exposed occurrences (all) | 5 / 61 (8.20%) 6 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported