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	• 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)	EMEA-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
Screen failure - exclusion criteria met	4
Consent withdrawn by subject	1

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	
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) Application site papules subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 10 / 61 (16.39%) 10 10 / 61 (16.39%) 10 7 / 61 (11.48%) 7		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 19 / 61 (31.15%) 23 18 / 61 (29.51%) 19 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