

**Clinical trial results:****An Open-label, Multicentre Study of the Safety of Twice Daily Oxycodone Hydrochloride Controlled-release Tablets in Opioid Experienced Children from Ages 6 to 16 Years Old, Inclusive, with Moderate to Severe Malignant and/or Nonmalignant Pain Requiring Opioid Analgesics.****Summary**

EudraCT number	2010-020471-23
Trial protocol	GB HU SK DE FI ES EE BE GR PL SE BG
Global end of trial date	29 July 2014

Results information

Result version number	v1 (current)
This version publication date	21 July 2016
First version publication date	07 August 2015
Summary attachment (see zip file)	OTR3001_Synopsis (otr3001-synopsis.pdf)

Trial information**Trial identification**

Sponsor protocol code	OTR3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01192295
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Purdue Pharma L.P
Sponsor organisation address	One Stamford Forum, Stamford, United States, CT 06901-3431
Public contact	Purdue Pediatric Call Centre, PRA International, +1 434 951 4115, PurduePediatric@praintl.com
Scientific contact	Purdue Pediatric Call Centre, PRA International, +1 434 951 4115, PurduePediatric@praintl.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2014
Global end of trial reached?	Yes
Global end of trial date	29 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to characterize the safety of oxycodone HCl CR tablets in opioid tolerant pediatric patients aged 6 to 16 years, inclusive, with moderate to severe malignant and/or nonmalignant pain requiring opioid therapy.

Protection of trial subjects:

An independent Data Monitoring Committee (DMC) was established to review the accumulating safety data from the trial. The DMC met periodically 6 times, during the course of the study to review safety data and make recommendations to Purdue Pharma L.P. regarding early stopping of the study, continuation of the study, or modification of the study protocol as needed.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	28 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Guatemala: 1
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	United States: 134
Country: Number of subjects enrolled	New Zealand: 2
Worldwide total number of subjects	155
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	27
Adolescents (12-17 years)	128
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Patient First Visit: 28 February 2011; Last Patient Last Visit: 29 July 2014. The study was conducted at medical/research sites in the United States, Spain, United Kingdom, Greece, Guatemala, Hungary, Israel, and New Zealand

Pre-assignment

Screening details:

Patients taking around-the-clock opioid medication for at least 5 consecutive days prior to taking the study drug and with at least 20 mg daily and no more than 240 mg daily of oxycodone or the equivalent for at least 48 hours before beginning the study

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open label study potential subjects were assigned a subject number at the time of screening

Arms

Arm title	Open label treatment
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Arm description:

Twice Daily Oxycodone Hydrochloride Controlled-release Tablets

Arm type	Experimental
Investigational medicinal product name	Oxycodone Hydrochloride Twice Daily Controlled-release Tablets
Investigational medicinal product code	Oxycodone HCl CR
Other name	NA
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Oxycodone HCl controlled-release (CR) twice daily tablets, at strengths of 10, 15, 20, 30, or 40 mg (20 to 240 mg daily), every 12 hours taken orally with water

Number of subjects in period 1	Open label treatment
Started	155
Completed	122
Not completed	33
Consent withdrawn by subject	7
Adverse event, non-fatal	10
Lost to follow-up	1
administrative reason	10
Lack of efficacy	5

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	155	155	
Age categorical			
NA			
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)	27	27	
Adolescents (12-17 years)	128	128	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	13.7		
standard deviation	± 2.33	-	
Gender categorical			
Units: Subjects			
Female	89	89	
Male	66	66	
RACE/Ethnicity			
Units: Subjects			
White	108	108	
Black or African American	38	38	
Asian	1	1	
Other	8	8	

Subject analysis sets

Subject analysis set title	age group 6 to <12 years
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Subject analysis set type	Safety analysis
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Subject analysis set description:
patients with ages 6 to <12 years

Subject analysis set title	age group >= 12 to <=16
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Subject analysis set type	Safety analysis
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Subject analysis set description:
Children with ages >= 12 to <=16

Reporting group values	age group 6 to <12 years	age group >= 12 to <=16	
Number of subjects	27	128	
Age categorical			
NA			
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)	27	0	
Adolescents (12-17 years)	0	128	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	9.6	14.5	
standard deviation	± 1.65	± 1.34	
Gender categorical			
Units: Subjects			
Female	14	75	
Male	13	53	
RAce/Ethnicity			
Units: Subjects			
White	20	88	
Black or African American	7	31	
Asian	0	1	
Other	0	8	

End points

End points reporting groups

Reporting group title	Open label treatment
Reporting group description: Twice Daily Oxycodone Hydrochloride Controlled-release Tablets	
Subject analysis set title	age group 6 to <12 years
Subject analysis set type	Safety analysis
Subject analysis set description: patients with ages 6 to <12 years	
Subject analysis set title	age group >= 12 to <=16
Subject analysis set type	Safety analysis
Subject analysis set description: Children with ages >= 12 to <=16	

Primary: Number of participants with Adverse Events as a Measure of Safety

End point title	Number of participants with Adverse Events as a Measure of Safety ^[1]
End point description: Safety assessments consisted of reports of AEs, Physical examinations, clinical laboratory tests results, vital signs measurements pulse oximetry (SpO2) and somnolence assessments. Safety variables were summarized descriptively within age group for the safety population. the safety population was the group of patients who received at least 1 dose of study drug during the study.	
End point type	Primary
End point timeframe: Up to 4 weeks (during the Study) and 7-10 days poststudy (safety follow-up assessment)	

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: no comparative inferential analysis is performed for the data from this open label study in which all patients received oxycodone HCI CR treatment. No adjustments for covariates are necessary for the analysis of this study. Data will be summarized overall and by age group where appropriate.

End point values	age group 6 to <12 years	age group >= 12 to <=16		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	128		
Units: Participants				
Serious adverse events	5	22		
All other adverse events in >=5% of patients	13	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Right Now Assessment by patients aged 6 to < 12

End point title	Pain Right Now Assessment by patients aged 6 to < 12
End point description: Pain right now was assessed by patients aged 6 to <12 years using the Faces of Pain Scale-Revised (FPS-R). the FPS-R is a horizontal row of 6 faces representing pain intensity, with "no hurt" at the far	

left and "hurts worst" at the far right; the 6 intensities are scored as 0, 2, 4, 6, 8 or 10 (the patient was not shown the numbers associated with the faces). A score of 0 means no pain, and a 10 means very much pain. Pain right now was assessed by the patient at screening, after the first dose, and , thereafter, twice daily during the AM and PM, approximately at the time of each (morning an evening) dose of oxycodone HCI CR tablets during the study treatment.

End point type	Secondary
End point timeframe:	
Baseline to Week 4	

End point values	age group 6 to <12 years			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline: number (n)= 27	4.44 (± 3.25)			
Average during week 1: morning, n=25	4.11 (± 2.674)			
Average during week 1: evening, n=26	4.07 (± 2.695)			
Average during week 2: morning, n= 23	3.66 (± 2.64)			
Average during week 2, evening, n=22	3.7 (± 2.686)			
average during week 3: morning, n=17	3.64 (± 2.579)			
Average during week 3: evening, n=17	3.76 (± 2.669)			
Average during week 4: morning, n=14	3.13 (± 2.569)			
Average during week 4: evening, n=14	3.42 (± 2.974)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Right Now Assessment by Patients aged >=12 to <=16 years

End point title	Pain Right Now Assessment by Patients aged >=12 to <=16 years
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End point description:

Pain right now was assessed by patients aged >=12 to <=16 years using a 100-mm visual analogic scale (VAS). the 100-mm line with 1 end marked "no pain" and the opposite end marked as "pain as bad as it could be". the patient was asked to make a mark on that line indicating his or her level of pain. the pain right now 100-mm VAS score was defined as the distance (in mm) from the "no pain" end to the patient's mark. The scale is measured on a 100 mm line: a 0 means no pain and bigger numbers indicate more pain. Pain right now was assessed by the patient at screening, after the first dose, and, thereafter, twice daily during the AM and PM, approximately at the time of each (morning and evening) dose of oxycodone HCI CR tablets during the study treatment

End point type	Secondary
End point timeframe:	
Baseline to week 4	

End point values	age group >= 12 to <=16			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: units on a scale				
arithmetic mean (standard deviation)				
baseline, n= 126	44.58 (± 28.291)			
Average during week 1: morning, n=124	40.38 (± 24.402)			
Average during week 1: evening, n=124	39.24 (± 23.301)			
Average during week 2: morning, n=122	34.49 (± 24.98)			
Average during week 2: evening, n=122	33.04 (± 24.778)			
Average during week 3: morning, n=101	32.56 (± 25.802)			
Average during week 3: evening, n=88	33.46 (± 24.639)			
Average during week 4: morning, n= 53	35.58 (± 27.177)			
Average during week 4: evening, n= 50	35.3 (± 26.711)			

Statistical analyses

No statistical analyses for this end point

Secondary: Use of supplemental Pain Medication

End point title	Use of supplemental Pain Medication
End point description:	Supplemental opioid and nonopioid pain medications were permitted during the study as deemed appropriate by the investigator. the dose of supplemental analgesic medication allowed was at the discretion of the investigator and within appropriate dose ranges for age and weight.
End point type	Secondary
End point timeframe:	Baseline to week 4

End point values	age group 6 to <12 years	age group >= 12 to <=16		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	128		
Units: participants				
Any supplemental pain medication	24	112		
Any opioid supplemental pain medication	21	93		
Any nonopioid supplemental pain medication	17	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Parent/Caregiver-Assessed Global Impression of Change (PGIC)

End point title	Parent/Caregiver-Assessed Global Impression of Change (PGIC)
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End point description:

The PGIC rating score variable was collected on a 7-point scale ranging from 1 to 7 (where 1=very much improved; and 7=very much worse). The PGIC is designed to assess overall satisfaction with the treatment. The number and percent of parent/caregivers reporting each category of PGIC response at the final visit was summarized for the safety population within age group

End point type	Secondary
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End point timeframe:

Baseline to week 4 or early discontinuation

End point values	age group 6 to <12 years	age group >= 12 to <=16		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	115		
Units: participants				
1=very much improved	10	42		
2= much improved	8	51		
3=minimally improved	3	15		
4=no change	3	5		
5=minimally worse	0	1		
6=much worse	0	0		
7=very much worse	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Parent/Caregiver assessed Functional Disability Inventory (FDI) for Patients aged 6 to <12 years

End point title	Parent/Caregiver assessed Functional Disability Inventory (FDI) for Patients aged 6 to <12 years
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End point description:

The FDI is a validated tool used to evaluate the degree to which children have reduced physical and psychosocial functioning because of their pain difficulties in the previous 2 weeks. The FDI comprises 15 items. Responses to each item were scored using a 5-point Likert scale. the individual scores are: (0) no trouble, (1) a little trouble, (2) some trouble, (3) a lot of trouble, and (4) impossible. A total score (ranging from 0 to 60) for the 15 items was calculated, with lower scores indicating less functional

disability. The FDI was performed by the parent/caregiver

End point type	Secondary
End point timeframe:	
Baseline to week 4	

End point values	age group 6 to <12 years			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline: n=26	27.1 (± 13.06)			
Week 4: n=25	23 (± 13.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parent/Caregiver Assessed Functional Disability Inventory (FDI) for Patients aged >=12 to <= 16 years

End point title	Parent/Caregiver Assessed Functional Disability Inventory (FDI) for Patients aged >=12 to <= 16 years
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End point description:

The FDI is a validated tool used to evaluate the degree to which children have reduced physical and psychosocial functioning because of their pain difficulties in the previous 2 weeks. The FDI comprises 15 items. Responses to each item were scored using a 5- point Likert scale. The individual scores are (0) no trouble, (1) a little trouble, (2) some trouble, (3) a lot of trouble, and (4) impossible. A total score (ranging from 0 to 60) for the 15 items was calculated, with lower scores indicating less functional disability. The FDI was performed by the parent/caregiver

End point type	Secondary
End point timeframe:	
Baseline to week 4	

End point values	age group >= 12 to <=16			
Subject group type	Subject analysis set			
Number of subjects analysed	128			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline: n=127	23.2 (± 17.47)			
Week 4: n=119	20.4 (± 12.65)			

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from start of study participation through the period beyond study completion

Adverse event reporting additional description:

AEs were learned of through spontaneous reports and/or patient interview, or were observed during physical examinations or other safety assessments. Ongoing AEs were followed until resolution or 30 days after last study drug dose. Serious AEs up to 30 days following the last study visit were followed until the AE or sequelae resolved or stabilized

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	Age group 6 to < 12 years
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Reporting group description:

Children 6 to < 12 years of age

Reporting group title	Age group >=12 to <=16
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Reporting group description:

Children >=12 to <=16 years of age

Serious adverse events	Age group 6 to < 12 years	Age group >=12 to <=16	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	22 / 128 (17.19%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	2 / 27 (7.41%)	5 / 128 (3.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory disorder			
subjects affected / exposed	1 / 27 (3.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	0 / 27 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Procedural pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 27 (3.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 27 (3.70%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Headache			
subjects affected / exposed	0 / 27 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion in childhood			
subjects affected / exposed	1 / 27 (3.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lethargy			

subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status migrainosus			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 27 (3.70%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	0 / 27 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis clostridial			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural cellulitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Age group 6 to < 12 years	Age group >=12 to <=16	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 27 (48.15%)	60 / 128 (46.88%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 27 (11.11%)	17 / 128 (13.28%)	
occurrences (all)	2	19	
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	11 / 128 (8.59%)	
occurrences (all)	0	12	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 27 (18.52%)	8 / 128 (6.25%)	
occurrences (all)	6	12	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 27 (22.22%)	26 / 128 (20.31%)	
occurrences (all)	12	51	
Nausea			

subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 6	20 / 128 (15.63%) 28	
Constipation subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 4	12 / 128 (9.38%) 12	
Skin and subcutaneous tissue disorders pruritus subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	7 / 128 (5.47%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2010	<ul style="list-style-type: none">-Reference to collect all opioid supplemental medication throughout the protocol was revised to include nonopioid supplemental medication since patients were allowed to use nonopioid supplemental medication for pain throughout the study.- Requirements for uptitration based on supplemental use was revised to have these criteria determined based on the investigator's judgment.- Collection of PCA doses and attempts was added to the protocol.- Method of obtaining temperature (oral) was deleted and a specific method was not specified.- Full analysis populations were made consistent between the synopsis and body of the protocol.- Typos/inconsistencies were corrected throughout the protocol.
27 January 2011	<ul style="list-style-type: none">- Added the collection of sparse PK sampling.- Added additional somnolence assessments for uptitration for additional safety measures.- Added additional conversion factors for fentanyl.- Added a phone call to occur every 48 hours for outpatients to collect safety information.- Added more detailed study drug dosing procedures clarifying how the study drug should be administered.- Added a bowel preparation to be performed before the start of dosing.- Added and revised additional inclusion and exclusion criteria: Clarified definition of opioid tolerant patient; postoperative patients cannot be enrolled until at least 120 hours after surgery; exclusion criteria regarding CYP3A4 inhibitors and the use of epidurals prior to study drug administration were clarified to make less stringent.- Revised laboratory requirements for day 1; clarified that local laboratory may be used for eligibility.- Added oxycodone as a prohibited supplemental analgesic medication since it would interfere with the analysis of study drug.- Increased the sample size to 135 patients in order to meet current minimum requirements for the number of pediatric patients to be exposed to study drug.- Changed opioid experienced to opioid tolerant throughout the protocol.

24 January 2012	<p>-The increase in the number of patients from 135 to 154 was made to account for the total number of patients required to be exposed to oxycodone for the evaluation of the safety of oxycodone in children, including all studies in our program;</p> <p>- For those patients who had undergone surgery, the postoperative criterion of waiting at least 120 hours from surgery to the start of study drug dosing was revised to at least 5 days.</p> <p>- language was included in the exclusion criteria of the protocol such that patients who had underlying gastrointestinal disorder predisposing them to obstruction were not enrolled in the study.</p> <p>-A washout period of at least 4 days for patient taking methadone prior to enroll into the study.</p> <p>- A conversion factor was added to convert the incoming dose of tramadol to oxycodone.</p> <p>-Recruitment of a urine pregnancy test, without the option of a serum pregnancy test, was added to visit 3 for patients who completed the OTR3001 study and were being screened to participate in the OTR3002 extension</p> <p>-The screening window was changed from up to 48 hours to up to 72 hours prior to Day 1 to allow adequate time for availability of laboratory results for review at the time that dosing initiation was planned.</p> <p>- Values used to define ranges of bilirubin displayed in listings and ranges of AST and ALT displayed in tables and listings were modified to be more inclusive and provide information on more patients with potentially clinically significant liver function test abnormalities.</p> <p>- Specified the volume (2 mL) of the tubes used for PK sampling.</p> <p>-Language for reporting of clinical supplies product complaints (protocol section 9.4.5) was updated to reflect the current process</p> <p>-Section 5.2 of the protocol was updated to reflect the most current ICH/GCP guidelines</p>
11 June 2012	<p>If a patient had difficulty getting to the site for a study visit, these visits might be conducted at a patient's home if the principal investigator deemed this to be appropriate based on the patient's medical status</p>
23 January 2014	<p>-A population PK analysis was conducted to determine whether additional PK samples would be required from the remaining patients to be enrolled into OTR3001. For this analysis, the final population PK data set included 255 pediatric patients with ages ranging from newborn to 16 years and weights from 2.4 to 112 kg. There were 99 patients included from OTR3001.</p> <p>- The major conclusions of these analyses were:</p> <ul style="list-style-type: none"> o The simulation based model evaluation shows a predictive ability for both pediatric and multiple dose adult oxycodone PK. o The results of this analysis demonstrated that exposures (Area under the curve at steady state [AUC_{ss}], maximum concentration in the dosing interval [C_{max}], minimum concentration in the dosing interval [C_{min}]) in 2 pediatric subgroups (ages >6 to <12 and ages 12 to 16 years) were similar by graphical comparison when the exposure was calculated both at the time of first dose and time of last dose. o At a weight-based oxycodone dose of 0.2 mg/kg, expected adult (age >16 years) exposure (AUC_{ss}) under the model was similar to pediatric (age 6 to 16 years) AUC_{ss}, with pediatric patients doses as in the clinical study. <p>- Based on these results, as described above, the decision was made to discontinue further collection of PK samples for this study; therefore, the PK sampling requirement was removed from the protocol.</p>

12 February 2014	<p>-A population PK analysis was conducted to determine whether additional PK samples would be required from the remaining patients to be enrolled into TR3001. For this analysis, the final population PK data set included 255 pediatric patients with ages ranging from newborn to 16 years and weights from 2.4 to 112 kg. There were 99 patients included from OTR3001.</p> <ul style="list-style-type: none">- The major conclusions of these analyses were:<ul style="list-style-type: none">o The simulation based model evaluation shows a predictive ability for both pediatric and multiple dose adult oxycodone PK.o The results of this analysis demonstrated that exposures (AUC_{ss}, C_{max}, C_{min}) in 2 pediatric subgroups (ages >6 to <12 and ages 12 to 16 years) were similar by graphical comparison when the exposure was calculated both at the time of first dose and time of last dose.o At a weight-based oxycodone dose of 0.2 mg/kg, expected adult (age >16 years) exposure (AUC_{ss}) under the model was similar to pediatric (age 6 to 16 years) AUC_{ss}, with pediatric patients' doses as in the clinical study.- Based on these results, as described above, the decision was made to discontinue - further collection of PK samples for this study; therefore, the PK sampling requirement was removed from the protocol
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported