Clinical trial results:
An Open-label, Extension Study to Assess the Long-Term Safety of Twice Daily Oxycodone Hydrochloride Controlled-release Tablets in Opioid Experienced Children Who Completed the OTR3001 Study

Summary

EudraCT number	2011-002235-26
Trial protocol	SE EE ES FI DE GR GB SK BE HU PL
Global end of trial date	09 December 2013

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)	OTR3002 Study report Synopsis (otr3002-synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	OTR3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01369615
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	04 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2013
Global end of trial reached?	Yes
Global end of trial date	09 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize the long-term safety of oxycodone HCl CR tablets in opioid experienced pediatric patients aged 6 to 17 years, inclusive, with moderate to severe malignant and/or non malignant pain requiring opioid therapy who completed the 4 -week treatment period in OTR3001.

Protection of trial subjects:

The DMC met periodically 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	05 January 2012
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	Israel: 1
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	23
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)	9
Adolescents (12-17 years)	14
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: 05 January 2012; Last Patient Last Visit: 09 December 2013. The study was conducted at 14 medical /research sites in the United States and Israel

Pre-assignment

Screening details:

Opioid-experienced pediatric patients with moderate ot severe malignant and/or nonmalignant pain requiring around the clock opioid therapy were eligible for open-lable Extension Study OTR3002 if they completed the 4-week treatment period Core Study OTR3001 and could benefit from continued treatment with oxycodone HCI CR 20 to 240 mg total daily

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 lable study potential subjects were assigned a subject number at the time of screening

Arms

Arm title	Open label treatment

Arm description:

Twice Daily Oxycodone Hydrochloride Controlled-release Tablets

Arm type	Experimental
Investigational medicinal product name	Oxycodone Hydrochloride Twice Daily Controlled-release
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	23
Completed	21
Not completed	2
Consent withdrawn by subject	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	23	23	
Age categorical 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)	9	9	
Adolescents (12-17 years)	14	14	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	12.6		
standard deviation	± 2.69	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	10	10	
Race/Ethnicity Units: Subjects			
White	16	16	
Black or African American	7	7	

Subject analysis sets	
Subject analysis set title	age group 6 to <12 years of age
Subject analysis set type	Safety analysis
Subject analysis set description: Children 6 to <12 years of age	
Subject analysis set title	age group >=12 to <=16 years of age
Subject analysis set type	Safety analysis
Subject analysis set description: Children 12 to <=16 years of age	

Reporting group values	age group 6 to <12 years of age	age group >=12 to <=16 years of age	
Number of subjects	9	14	

Age categorical 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)	9	0	
Adolescents (12-17 years)	0	14	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	9.9	14.3	
standard deviation	± 1.76	± 1.49	
Gender categorical Units: Subjects			
Female	6	7	
Male	3	7	
Race/Ethnicity Units: Subjects			
White	6	10	
Black or African American	3	4	

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 of age
Subject analysis set type	Safety analysis
Subject analysis set description: Children 6 to <12 years of age	
Subject analysis set title	age group >=12 to <=16 years of age
Subject analysis set type	Safety analysis
Subject analysis set description: Children 12 to <=16 years of age	

Primary: Number of patients with adverse events as a mesure of safety

End point title	Number of patients with adverse events as a mesure of

End point description:

Safety assessments included adverse events (AEs), vital sign measurements, clinical laboratory test results, and somnolence (University of Michigan Sedation Scale (UMSS)). Safety variables were summarized descriptively within age group for the extension safety population

End point type	Primary

End point timeframe:

Up to 6 months (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-lable study in wich all patients receive 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 of age	age group >=12 to <=16 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	14		
Units: participants				
Serious adverse events	3	2		
All other AE in more or equal than 5% of patients	8	8		

Statistical analyses

No statistical analyses for this end point

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/30 days after last study drug dose. SAEs up to 30 days following the last study drug visit were followed until the AE or sequelae resolved or stabilized

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	6 to < 12 years

Reporting group description:

children 6 to < 12 years

Reporting group title	>=12 to <=16 years

Reporting group description:

Children >=12 to <=16 years

Serious adverse events	6 to < 12 years	>=12 to <=16 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	2 / 14 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
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	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
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	0 / 9 (0.00%)	1 / 14 (7.14%)	
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	6 to < 12 years	>=12 to <=16 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	8 / 14 (57.14%)	
Vascular disorders			
flushing			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			

Scar excision			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Cyst			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	2	
Inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 9 (33.33%)	2 / 14 (14.29%)	
occurrences (all)	4	2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
atelectasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	
occurrences (all)	1	1	

Epistaxis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Respiratory depression			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	1	
Respiratory distress			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Oxygen saturation decreased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Respiratory rate			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			

subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
weight decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	4	
Sedation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Lymphadenopathy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Auricular swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
External ear pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	

Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Mydriasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	
occurrences (all)	1	4	
Oral pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 9 (22.22%)	2 / 14 (14.29%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
dry skin			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Photosensitivity reaction			

subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	2	1	
Rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Scar			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Seborrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
urinary tract infection			

subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	1	
Vaginal infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2011	A. Provide more specific instructions for post-study opioid management, including a tapering procedure for patients no longer requiring opioid treatment and a method of conversion to other opioids. B. Provide specific instructions for down-titration during the study to avoid potential opioid withdrawal syndrome.
24 January 2012	A. To increase the number of patients from 135 to 154 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 the program. B. To clarify that only a limited number of patients were expected to complete OTR3001 and enter OTR3002. C. Based on spontaneous post-marketing reports, including reports of intestinal obstruction and exacerbation of diverticulitis, warnings and precautions were added to the OxyContin® package insert in Oct 2011 advising physicians to use caution when prescribing OxyContin® to patients who have an underlying gastrointestinal disorder predisposing them to obstruction. To ensure adherence with the guidelines added to the package insert, similar language was included in the exclusion criteria such that patients who were predisposed to these types of conditions would not be enrolled into the study. D. To correct an error and clarify that somnolence assessments would be performed by the parents/caregivers, rather than the patients. E. To modify the values used to define ranges of bilirubin displayed in listings to be more inclusive and provide information on more patients with potentially clinically significant bilirubin levels F. To revise the language in various sections as, in most cases, data would be presented only for the extension safety population and to clarify when data from OTR3001 would be included in the summary analyses. G. To update language for reporting of CSPCs to reflect the current process.
11 June 2012	The amendment was submitted only to sites that requested it. The rationale for the amendment was the following: A. To allow patients having difficulty getting to the site for a visit to have the visits conducted at the patient's home if deemed appropriate by the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrollement for study OTR3002 was closed by Purdue Pharma L.P on 01-January-2014 due to administrative reasons not related to safety. Interpretation is limited by the samall number of patients in each age group in this study

Notes: