Clinical trial results:
RCT comparing the analgesic efficacy of 4 therapeutic strategies based on 4 different major opioids (fentanyl, oxycodone, buprenorphine vs morphine) in cancer patients with moderate/severe pain, at the moment of starting 3rd step of WHO analgesic ladder.

Summary

EudraCT number	2010-021017-23
Trial protocol	IT
Global end of trial date	31 July 2014

Results information

Result version number	v1 (current)
This version publication date	28 March 2019
First version publication date	28 March 2019
Summary attachment (see zip file)	Study results (study results CT.GOV_CERP.pdf)

Trial information

Trial identification

Sponsor protocol code	STUDIO CERP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01809106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mario Negri Institute for Pharmacological Research
Sponsor organisation address	Via G. La Masa 19, Milan, Italy, 20156
Public contact	Oscar Corli, Mario Negri Institute for Pharmacological Research, oscar.corli@marionegri.it
Scientific contact	Oscar Corli, Mario Negri Institute for Pharmacological Research, oscar.corli@marionegri.it

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• The comparison of the analgesic efficacy of 4 treatment strategies based on 4 different strong opioids (oral morphine and oxycodone, transdermal fentanyl and buprenorphine) administered by randomization during a 4 weeks follow-up period, in patients with moderate to severe pain due to the cancer, measured at each visit by means of a NRS 0 to 10, and related to the average pain of the previous 24 hours.

Protection of trial subjects:

It was run according to the Declaration of Helsinki of Good Clinical Practice. Regulatory agencies and local ethics committees approved the study protocol. All patients gave written informed consent.

Background therapy:

--

Evidence for comparator: -

Actual start date of recruitment	31 May 2011
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	Italy: 518
Worldwide total number of subjects	518
EEA total number of subjects	518

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)	0
Adults (18-64 years)	350
From 65 to 84 years	168

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 44 sites in Italy from May 2011 to July 2014.

Pre-assignment

Screening details:

520 patients were randomized and 498 were included in ITT analysis

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active comparator

Arm description:

Morphine

Arm type	Active comparator
Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg/day

Arm title	Experimental

Arm description:

Oxycodone

Arm type	Experimental
Investigational medicinal product name	Oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

40 mg/day

Arm title	Experimental

Arm description:

Buprenorphine

Arm type	Experimental
Investigational medicinal product name	Buprenorphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

35 µg/h

Arm title	Experimental

Arm description:

Fentanyl

Arm type	Experimental
Investigational medicinal product name	Fentanyl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

25 µg/h

Number of subjects in period 1	Active comparator	Experimental	Experimental
Started	130	130	130
Completed	122	125	127
Not completed	8	5	3
Never received treatment	1	1	-
Lack of efficacy	7	4	3

Number of subjects in period 1	Experimental
Started	128
Completed	124
Not completed	4
Never received treatment	4
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Active comparator
Reporting group description:	
Morphine	
Reporting group title	Experimental
Reporting group description:	
Oxycodone	
Reporting group title	Experimental
Reporting group description:	
Buprenorphine	
Reporting group title	Experimental
Reporting group description:	
Fentanyl	

Reporting group values	Active comparator	Experimental	Experimental
Number of subjects	130	130	130
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	67.5	66.9	65.2
standard deviation	± 11.7	± 11.1	± 13.5
Gender categorical			
Units: Subjects			
Female	59	56	60
Male	71	74	70

Reporting group values	Experimental	Total	
Number of subjects	128	518	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	

Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	68		
standard deviation	± 10.6	-	
Gender categorical			
Units: Subjects			
Female	56	231	
Male	72	287	

Subject analysis sets

Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

the intention-to-treat (ITT) population, which included all randomized patients without major violations of the eligibility criteria and with at least one pain evaluation after baseline.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Only patients who started on opioid were included in the safety analysis, which considered patients in the arm of the treatment they actually received. Each patient was considered until the end of the 28-day follow-up, or until a switch or premature discontinuation of the study for any reason.

Reporting group values	ITT analysis set	Safety	
Number of subjects	498	515	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	66.9		
standard deviation	± 11.8	±	
Gender categorical			
Units: Subjects			
Female	221	229	
Male	277	286	

End points

End points reporting groups

Reporting group title	Active comparator
Reporting group description: Morphine	
Reporting group title	Experimental
Reporting group description: Oxycodone	
Reporting group title	Experimental
Reporting group description: Buprenorphine	
Reporting group title	Experimental
Reporting group description: Fentanyl	
Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat
Subject analysis set description: the intention-to-treat (ITT) population, which included all randomized patients without major violations of the eligibility criteria and with at least one pain evaluation after baseline.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: Only patients who started on opioid were included in the safety analysis, which considered patients in the arm of the treatment they actually received. Each patient was considered until the end of the 28-day follow-up, or until a switch or premature discontinuation of the study for any reason.	

Primary: Proportion of Non-Responder (NR) Participants

End point title	Proportion of Non-Responder (NR) Participants
End point description: Evaluation of the proportion of Non-Responder (NR) participants. NR correspond to the subjects who do not report any analgesic effects, with a P.I.D. (pain intensity difference) from visit 6 and visit 1 =/< 0%, (using a 0-10 NRS). It includes the situations of average pain intensity "stable" or "worsened" at day 28 compared with baseline values.	
End point type	Primary
End point timeframe: 28 days	

End point values	Active comparator	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	125	127	124
Units: Number of patients	14	18	14	11

End point values	ITT analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	498			

Units: Number of patients	57			

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The χ2 test (or Fisher's exact test, where appropriate) was used to assess differences between oral oxycodone, TD buprenorphine or TD fentanyl, compared with oral morphine.

Comparison groups	Experimental v Experimental v Experimental v Active comparator
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Proportion
Variability estimate	Standard deviation

Secondary: Proportion of Full-responder

End point title	Proportion of Full-responder

End point description:

Evaluation of the proportion of subjects who report full analgesia (full responders: FR). FR is operationally defined as a patient with a P.I.D. =/> 30% from visit 6 and visit 1 (NRS 0 to 10).

End point type	Secondary

End point timeframe:

28 days

End point values	Active comparator	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	125	127	124
Units: Number of patients	89	90	95	88

End point values	ITT analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	498			
Units: Number of patients	362			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Opioid Escalation Index

End point title	The Opioid Escalation Index

End point description:

The proportion of subjects with an increase of opioid daily dose > 5% compared with the basal dosage (OEI%).

End point type	Other pre-specified

End point timeframe:

28 days

End point values	Active comparator	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	122	125	127	124
Units: Number of participants	13	24	18	45

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4 weeks

Assessment type	Non-systematic

Dictionary used

Dictionary name	NA
Dictionary version	0

Reporting groups

Reporting group title	Adverse events

Reporting group description: -

Serious adverse events	Adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 515 (2.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Hyperalgesia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Exitus			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Decline general condition			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperpirexia			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Bowel occlusion			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oral cavity bleeding			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic disorder			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	1 / 515 (0.19%)		
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	Adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	404 / 515 (78.45%)		
General disorders and administration site conditions			

Drowsiness			
subjects affected / exposed	304 / 515 (59.03%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	221 / 515 (42.91%)		
occurrences (all)	1		

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? Yes

Date	Interruption	Restart date
31 July 2014	In September 2014, in view of the disappointing recruitment, the Steering Committee decided to early stop enrollment, fully aware that the study could lose the power to test the planned differences between treatments.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26940689

http://www.ncbi.nlm.nih.gov/pubmed/29220110