Clinical trial results:
A POPULATION STUDY INTO THE PREVALENCE AND GENETIC PROFILE OF PATIENTS WITH CHRONIC PAIN WHO DO NOT RESPOND TO ORAL CODEINE
A single site, pilot population study into the prevalence and genetic profile of patients with chronic pain who do not respond to oral codeine.

Summary

EudraCT number	2007-006184-70
Trial protocol	GB
Global end of trial date	01 October 2014

Results information

Result version number	v1 (current)
This version publication date	07 March 2020
First version publication date	07 March 2020
Summary attachment (see zip file)	CODEINE_NONRESPONDER (Clinical_Study_Report_CODEINE_NONRESPONDER_STUDY_FINAL_24_3_15.pdf)

Trial information

Trial identification

Sponsor protocol code	PM07/8404

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Leeds Teaching Hospitals NHS Trust
Sponsor organisation address	St James University hospital, Leeds, United Kingdom, LS9 7TF
Public contact	Pain Management department, The Leeds Teaching Hospitals NHS Trust, +44 01132063132, helen.radford@leedsth.nhs.uk
Scientific contact	Pain Management department, The Leeds Teaching Hospitals NHS Trust, +44 01132063132, helen.radford@leedsth.nhs.uk

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	01 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2014
Global end of trial reached?	Yes
Global end of trial date	01 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Determine the proportion of chronic pain patients who lack an analgesic response to codeine (i. e. codeine non-responders)

- Investigate whether the proportion of codeine non-responders in the chronic pain population is greater than the well known figure of 10% seen in the general population

Protection of trial subjects:

The described study will be conducted in compliance with the protocol, The Research Governance Framework, the principles of GCP, Directive2001/20/EC and associated regulatory (MHRA) regulations, and all applicable Leeds Teaching Hospitals NHS Trust research requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2008
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 Kingdom: 131
Worldwide total number of subjects	131
EEA total number of subjects	131

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)	131
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A sample of 131 Caucasian, persistent non-malignant pain patients were recruited from the Pain Clinic at Seacroft Hospital Leeds during October 2009 to June 2014. All potential participants were diagnosed by a Pain Management Consultant with neuropathic or nociceptive persistent pain for greater than six months.

Pre-assignment

Screening details:

Potential study participants were identified from the current patient database held by pain services or directly from clinic by their pain consultant. participants were contacted and invited to participate by post. Each potential participant received a letter of invitation, the REC approved PIS and consent form 14 days prior to first visit

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline Arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Codeine Phosphate 30mg
Investigational medicinal product code	
Other name	Codeine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients will receive 28 tablets of 30mg codeine phosphate in a blister pack to be taken orally. The patient will be instructed to take 30mg (1 tablet) every 4 hours (up to a maximum of 120mg in 24 hours). Extra tablets (Eight) will also be provided in the blister pack in case of loss.

Arm title	End Data

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Codeine Phosphate 30mg
Investigational medicinal product code	
Other name	Codeine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients will receive 28 tablets of 30mg codeine phosphate in a blister pack to be taken orally. The patient will be instructed to take 30mg (1 tablet) every 4 hours (up to a maximum of 120mg in 24 hours). Extra tablets (Eight) will also be provided in the blister pack in case of loss.

Number of subjects in period 1	Baseline Arm	End Data
Started	1	130
Completed	1	130

Baseline characteristics

Reporting groups

Reporting group title	Main Trial Period

Reporting group description: -

Reporting group values	Main Trial Period	Total	
Number of subjects	131	131	
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	56.17		
standard deviation	± +13.88	-	
Gender categorical Units: Subjects			
Female	79	79	
Male	52	52	

End points

End points reporting groups

Reporting group title	Baseline Arm
Reporting group description: -	
Reporting group title	End Data
Reporting group description: -	

Primary: 30% reduction in mean “average pain” score

End point title	30% reduction in mean “average pain” score[1]

End point description:

Only 25% of EM phenotypes (AS 1. 1.5 and 2) reached ≥30% reduction in mean “average pain” in the last 24 hours measured on a 0-10 NRS scale when compare to baseline and categorised as a codeine responder.

End point type	Primary

End point timeframe:

the last 24 hours measured on a 0-10 NRS scale when compare to baseline and categorised as a codeine responder.

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: Please see attached final study report for details of all statistical analysis's performed in the trial.

End point values	Baseline Arm	End Data		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	130		
Units: Number of patients	1	31		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events by the participants through the pain diary or verbally at study visits. No SAE's were reported in the study. For details of all AE's, please see section 12, tables 34 & 35 of the attached final study report, and page 41 for a summary.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: For details of all adverse events, please see page 41 of the attached study report for a lay summary, and section 12, tables 34 & 35 of the attached final study report for details of all AE's in a tabular format.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2010	Addition of poster advert, no change to protocol. Approved poster placed in Pain Clinics to aid study awareness and improve study accrual
08 December 2011	Removal of oral transudate testing. Interim analysis conducted on 20 oral transudate samples to assess phenotyping suitability. Analysis confirmed this method ineffective at predicting CYP2D6 phenotypes and removed from study design.
14 August 2012	Change to inclusion criteria. To allow potential participants to be recruited who have daily worse pain either equal to or greater than 4/10 on Numerical Rating Scale (such as the BPI), but whose average daily pain may be lower than 4/10. Patients commented to the research team that due to the nature of their chronic pain they find it difficult to average out their daily pain score. Therefore by using the worst pain score in the last 24 hours these patients would be able to be included in the study. This change will have no detrimental effect on the study or the data as the primary endpoint is the pain scores to determine the proportion of patients who are non-responders to codeine. The definition of a non-responder will remain a patient who does not display a reduction in pain scores of 30% or more over the course of 5 days.

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.

The age breakdown for all participants in sections 1 & 3 were not available at the time of upload, as all members of the research team have left LTHT . Should this information become available, this will be added to the record.

Notes: