



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, Directive 2001/20/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 $\geq 30\%$ reduction in mean "average pain" in the last 24 hours measured on a 0-10 NRS scale when compared 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 compared 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: