Pain And Interventional Neuromodulation (PAIN)Research Group

Clinical Study Report

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.

(Protocol: A2007N)

[MARCH 2015]

CONFIDENTIAL

SIGNATURE PAGES FOR CLINICAL STUDY REPORT

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed:  Date: 26/8/15

Print Name: Dr K Simpson

Role in Trial: Chief Investigator

Address: PAIN Research Group, D Ward Seacroft Hospital, Leeds

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1 TITLE PAGE

Study Title: A POPULATION STUDY INTO THE PREVALENCE AND GENETIC PROFILE OF PATIENTS WITH CHRONIC PAIN WHO DO NOT RESPOND TO ORAL CODEINE

Name of Test Drug: Codeine Phosphate 30mg

Indication Studied: Codeine non response in patients suffering from persistent pain

Study Description: A single site, pilot population study into the prevalence and genetic profile of patients with chronic pain who do not respond to oral codeine.

Sponsors: The Leeds Teaching Hospitals NHS Trust

Protocol: PM07/8404

Clinical Phase: IV

Study Dates: October 2009 - June 1014

Investigators: Dr K Simpson; Ms H Radford

GCP Statement: This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents

Date of Report: 24th March 2015

2 SYNOPSIS

NAME OF SPONSOR: LTHT **NAME OF FINISHED PRODUCT** N/A **NAME OF ACTIVE INGREDIENT(S)** Codeine Phosphate	**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD** Volume: N/A Page: N/A	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of Study	A POPULATION STUDY INTO THE PREVALENCE AND GENETIC PROFILE OF PATIENTS WITH CHRONIC PAIN WHO DO NOT RESPOND TO ORAL CODEINE		
Investigator(s)	Dr K Simpson; Ms H Radford		
Study centre(s)	Pain Services, D Ward Seacroft Hospital, York Road, Leeds LS14 6UH		
Publication	N/A		
Study period	From: October 2009 To: June 2014	Phase of development	Phase IV
Objectives	Primary Objective: 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 Secondary Objective: Investigate whether codeine non-responsiveness is different in nociceptive, neuropathic and mixed pain states Correlate genetic testing from saliva samples for CYP2D6 plus urine and oral fluid testing of morphine metabolites as predictors of codeine non-responsiveness Investigate the pharmacogenetics of codeine phosphate and its implications in clinical practice for chronic pain clinic attendees		
Methodology	Single centre, prospective, open label study design		
Number of patients	Planned: 150 (sample size of 121 subjects will give 90% power) Analysed: 131 (enrolled group) from which 125 full data sets were analysed.		
Diagnosis and main criteria for inclusion	Male or female, Caucasian, aged between 18-80 years with a persistent moderate to severe pain condition greater than 3 months duration that had been diagnosed by a pain management specialist		
Test product, dose and mode of administration	Oral Codeine Phosphate 30mg, one tablet four times a day		
Duration of treatment	Five days		
Criteria for evaluation	Primary: The primary endpoint is the patient's status as a codeine responder or non-responder and CYP2D6 genetic phenotype. Secondary: The secondary endpoints, BPI, SLANSS and Global Impression of Change,		
Statistical methods	The overall population estimate of the proportion of responders will be estimated and 95% confidence intervals will be produced using the exact binomial distribution. The responder/non-responder status will be tabulated against the four genetic groups. Logistic regression will be used to formally compare the proportions. The log-transformed levels of the codeine metabolites measured in urinalysis will be summarized for responders and non-responders, and also for the four genetic groups		

	and oral fluid, using means, SDs, medians and range and using box-and-whisker plots. ANOVA will be used on each log-transformed metabolite to compare the four genetic groups. Logistic regression will be used with the log-transformed levels of the metabolites as covariates to predict the responder/non-responder status. A multivariate logistic regression model that combines the genetic group and the log-transformed metabolite levels to predict responder/non-responder status will be fitted. The suitability of the model as predictor of responder/non-responder status will be assessed using ROC curves. Secondary Analyses The secondary endpoints, m-BPI-sf, SLANSS and Global Impression of Change, will be summarised by responder/non-responder status and by genetic group in terms of means, SDs, median and range.

NAME OF COMPANY : LTHT **NAME OF FINISHED PRODUCT** N/A **NAME OF ACTIVE INGREDIENT(S)** Codeine Phosphate	**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD** Volume : N/A Page: N/A	**(FOR NATIONAL AUTHORITY USE ONLY)**

SUMMARY CONCLUSIONS

The main findings of this study are as follows:

- 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.
- The frequency of IM phenotypes in this sample is considerable smaller than expected in a general population
- Codeine response could be predicted with 79% accuracy using a novel prediction model scoring system based on urinary total morphine metabolites concentrations (model 3) and morphine:creatinine ratio from day 4 urine samples collected during day0-day5 oral codeine 30mg QDS for persistent pain.

DATE OF THE REPORT: 24th March 2015

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4 LIST OF ABBREVIATIONS & DEFINITION OF TERMS

AE: Adverse Event

ADR: Adverse Drug Reaction

ALT: Alanine Aminotransferase

AS: CYP2D6 Activity Score

AST: Aspartate Aminotransferase

ANOVA: Analysis of Variance

BPI: Brief Pain Inventory (questionnaire)

CGIC: Clinician's global impression of change

CRF: Case Report Form

CTIMP: Clinical Trial of Investigational Medicinal Product

CYP2D6: Cytochrome P40 family 2, sub family D, polypeptide 6

DDI: Drug to Drug Interaction

EM: CYP2D6 Extensive Metaboliser

GCP: Good Clinical Practice

GLP: Good Laboratory Practice

GP: General Practitioner

HLQ: Higher Limit of Quantification

ICH: International Conference on Harmonisation

IM: CYP2D6 Intermediate Metaboliser

IMP: Investigational Medicinal Product

ITT: Intention to Treat

ISRCTN: International Standard Randomisation Clinical Trial Number

LC-MS/MS: Liquid Chromatography with Tandem Mass Spectroscopy

LLQ: Lower Limit of Quantification

LTHT: Leeds Teaching Hospitals NHS Trust

MHRA: Medicines & Healthcare Regulatory Authority

NIHR: National Institute of Health Research

NIMP: Non Investigational Medicinal Product

NRS: Numerical Rating Scale

NSAID: Non-steroidal Anti-inflammatory Drug

PM: CYP2D6 Poor Metaboliser

SLANSS: Leeds Assessment of Neuropathic Signs and Symptoms (questionnaire)

QDS: Quater die sumendus (four times a day)

QA: Quality Assurance

PIS: Participant Information Sheet

PGIC: Patient's Global Impression of Change

REC: Regional Ethics Committee

ROC: Receiver Operating Characteristic Curve

RSA: Research Sponsorship Agreement

SAE: Serious Adverse event

SD: Standard deviation

SLANSS: Self-reported Leeds Assessment of Neuropathic Pain Signs & Symptoms

TMF: Trial Master File

UKCRN: UK Clinical Trials Network

UM: CYP2D6 Ultra-rapid Metaboliser

WHO: World Health Organisation

5 ETHICS AND REGULATORY APPROVAL

5.1 INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments (Appendix 14.1), and the patient information sheet (Appendix 14.2) were reviewed and approved by the appropriate independent ethics committees as detailed in table one below.

Table 1: Ethics committees

Centre name and number	PAIN Research Group (Leeds)
Investigator	Dr K Simpson/ Ms H Radford
Ethics committee	Leeds East (Type 2, CTIMP flagged) Research Ethics Committee (REC)
Chairman	Mr Jon Silcock
Date of approval of the final protocol	09th January 2009
Date of approval of amendment 1	15th April 2010
Date of approval of amendment 2	4th January 2012
Date of approval of amendment 3	29th October 2012

5.2 ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the current version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practise (GCP).

5.3 PATIENT INFORMATION AND CONSENT

All patients provided written informed consent to participate in the study prior to being screened. The patient information sheet detailed the procedures involved in the study (aims, methodology. potential risks, anticipated benefits) and the investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patient was then allowed time to consider the information presented before signing and dating the informed consent form (Appendix 14.3) to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records.

5.4 REGULATORY APPROVAL

The study was performed in compliance with the requirements of the MHRA. The study gained full regulatory approval from the on 12/12/2008 (Appendix 14.4); The Leeds Teaching Hospitals (LTHT) was issued with the following EudraCT number [2007-006184-70]. The study gained full approval from Leeds East (Type 2, CTIMP flagged) Research Ethics Committee on 09/01/2009 (Appendix 14.5).

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table 2 shows the principal study personnel involved in the study.

Table 2: Principal study personnel

Title	Name and affiliation
Principal investigator	Dr K Simpson (LTHT)
Sponsor	The Leeds Teaching Hospitals NHS Trust (LTHT)
Project Managers	Mrs H Radford (University of Leeds/LTHT)
Clinical Research Associate(s)	Jessie Bridson (LTHT)
Medical Adviser	N/A
Laboratory investigator	Dr E Fox (LTHT)
Data Management	Mrs H Radford (University of Leeds/LTHT)

7 INTRODUCTION

Pharmacogenetics is the study of the dissimilarity in inter-individual response to drugs as the consequence of genetic differences. Clinical disparity in drug response may be as a result of pharmacokinetics or pharmacodynamics or it may be idiosyncratic. These differences may have a genetic basis. An example of this might be the situation where an individual has a suboptimal or even a complete lack of therapeutic response to a drug. The ability to predict clinical efficacy and identify these variations through an easily executed, repeatable, cost effective clinical test would be a valuable tool. The benefits may include enhanced patient compliance due to better clinical response, improved patient safety, and reduced costs: ultimately it may be seen as a step towards tailoring medical management to the individual[1].

7.1 MANAGEMENT OF CHRONIC PAIN

Chronic pain was originally defined as pain that has lasted 6 months or longer. More recently it has been defined as pain that persists longer than the temporal course of natural healing that is associated with a particular type of injury or disease process[2]. The International Association for the Study of Pain defines pain as an unpleasant sensory and affective experience induced by the exposure to noxious stimuli i.e. injury incipient or substantive in nature[3].

Chronic pain may be related to a number of different medical conditions including diabetes, arthritis, migraine, previous trauma or injury and may worsen in response to environmental

and/or psychological factors. There are a variety of treatment options for people with chronic pain. The goal of pain management is to provide symptom relief and improve an individual's level of functioning in daily activities.

A number of types of analgesics are used in the management of chronic pain, including COX-2 inhibitors, antidepressants, and opioids. Prescription of analgesics in the pain clinic follows the World Health Organisation Pain Relief ladder[4]. This is a three step approach to pain management. Step one is a non-opioid medication, step two is an opioid for mild to moderate pain and step three is an opioid for moderate to severe pain. Patients presenting with chronic pain are commenced on step one of the analgesic ladder which is usually Paracetamol 1g every 4 hours. If the patient is still reporting significant pain after 2 weeks, it is common to proceed to a step two analgesic, particularly Codeine (up to 60mg every 4 hours) [5].

7.2 RATIONALE FOR THE STUDY

Opioid analgesia is due mainly to pharmacological action on mu-opioid receptors. Morphine, a strong opioid, acts directly on these receptors to produce its analgesic effect. However, the strong opioid Tramadol and weak opioid Codeine have limited direct pharmacological effect on mu-receptors. Tramadol and Codeine analgesic efficacy is dependent upon a proportion of the dose being converted to active metabolites by hepatic phase-1 metabolism. The enzyme responsible for this biotransformation, CYP2D6, is a member of the cytochrome P450 super-family (CYP450) of oxidative enzymes collectively responsible for the phase-1 metabolism of the majority of prescription drugs [6-11.]

The *CYP2D6* gene encoding the CYP2D6 enzyme is highly polymorphic leading to four identified CYP2D6 phenotypes of poor (PM), intermediate (IM), extensive (EM) and ultra-rapid (UM) metabolisers. Assessment of individual's inferred CYP2D6 phenotype can be undertaken either by clinical assessment or CYP2D6 genotyping. Clinical assessment involves observing the individual's characteristics combined with influences of any present environmental factors[12]. This can be conducted using a CYP2D6 prodrug or substrate and measuring the bio-transformed active metabolite concentrations present in urine, blood, saliva or breath test at a selected time point post dose.

It has been identified that due to non-functional or reduced enzyme activity, CYP2D6 PM and IM phenotypes have limited ability to bio-transform Codeine and Tramadol to their pharmacological active metabolites and therefore may lack therapeutic analgesic response. CYP2D6 PM and IM phenotypes are also at risk of adverse drug reactions (ADRs) from higher than expected plasma concentrations of prescribed CYP2D6 substrates such as pain adjuvant Amitriptyline due to limited CYP2D6 metabolism. Individuals possessing the CYP2D6 UM phenotype are also at risk of lack of therapeutic efficacy and ADRs. CYP2D6 UMs have higher than expected enzyme function through duplications of fully functional CYP2D6 alleles. The higher level of CYP2D6 function bio-transforms Codeine and Tramadol rapidly, leading to the risk of toxicity from higher than expected active metabolite plasma concentrations and lack of maintained analgesic effect.

The clinical implications of CYP2D6 polymorphisms resulting in PM, IM and UM phenotypes have been well studied. The prevalence of CYP2D6 polymorphisms resulting in PM, IM and UM phenotypes in a Caucasian population have been estimated at up to 33% of the general population [6,8,10,11,13-17]. However Jannetto and Bratanow (2009)[18] found that in a 61 Caucasian persistent pain patients the prevalence of PM, IM and UM phenotypes were 46%. Therefore further research is needed to investigate if there is a higher incidence of these phenotypes in a persistent pain patient population which may provide evidence that CYP2D6 screening is clinically appropriate to improve patient outcomes.

CYP2D6 screening is not part of current clinical practice in the UK for numerous reasons such as infrastructure, cost effectiveness and clinical utility. To aid clinical translation of CYP2D6 screening a method of inferring an individual's phenotype without genotyping would provide a clinical tool to prescribing decisions at the point of care. Prodrugs such as Dextromethorphan, Debrisoquine or Sparteine are not readily available to clinicians to use as CYP2D6 phenotyping agents and Tramadol would be an unsuitable choice in a persistent pain population due to its strong opioid classification. A more suitable choice of CYP2D6 phenotyping agent would be the commonly prescribed prodrug Codeine.

Kirchheiner et al., (2006)[19] found CYP2D6 phenotype could be confidently inferred for PM (AS 0), EM (AS 1.5, AS 2) and UM (AS 2.5, AS 3) but not for IM (AS 0.5) or EM (AS 1) from a 0-6h urine collection post 30 mg codeine doses. Further research is required to establish if accurate CYP2D6 phenotyping from urinary codeine O-demethylation metabolites can be more easily conducted from a simpler sampling method such as a single urine collection post oral dose. This

would be a more feasible method of CYP2D6 screening at the point of care. Analysis of codeine O-demethylation metabolites in oral fluid samples is another potential phenotyping method that could be used in CYP2D6 screening at the point of care. Analysis of oral fluid for codeine O-demethylation metabolites has not been previously investigated as a method to infer CYP2D6 phenotype and therefore needs to be explored further.

The benefits of improved patient outcomes and reduced drug reactions by tailoring clinical prescribing decisions to an individual's CYP2D6 phenotype have been demonstrated in case studies[20-25]. Multiple studies have been conducted investigating drug to drug interactions (DDIs) and CYP2D6 phenocopying/autophenocopying resulting in confirmed magnitude of inhibition for certain drugs[26]. The accumulation of this evidence led to the first systematic review conducted by Swen et al., (2008)[27] to produce 21 prescribing guidelines related to CYP2D6 phenotype and substrates/prodrugs used in a variety of therapeutic areas. The analgesic drugs Tramadol, Oxycodone, Nortriptyline, Duloxetine and Codeine were included in these prescribing guidelines. With the exception of Duloxetine, Swen et al., (2008)[27] recommended selecting an alternative analgesic if considering prescribing Tramadol, Oxycodone, Nortriptyline, and Codeine for CYP2D6 PM, IM and UM phenotypes.

Although clinically useful, prescribing guidelines are only practical to clinicians if they are able to infer their patient's CYP2D6 phenotype in a clinical setting. In a recent audit conducted in Pain Services Seacroft Hospital, 58.7% of patients with persistent pain referred by their GP to a specialist pain management were prescribed at least one analgesic reliant on CYP2D6 for therapeutic efficacy. The audit also found that nearly 30% of patients referred for specialist pain management were co-prescribed at least one CYP2D6 inhibitor with at least one analgesic reliant on CYP2D6 function with a risk of clinically significant potential drug to drug interactions (DDIs) in 19.9% referrals and suboptimal analgesia in 18.7%. If CYP2D6 screening could be conducted in a reliable, easily executed and cost effective manner, clinical CYP2D6 prescribing guidelines may be more actively utilised by prescribers improving patient's outcomes and reduce unnecessary ADRs. Therefore there is a need to investigate further the proportion of patients that CYP2D6 screening could benefit and determine a cost effective method of inferring phenotype that is easily utilised in a clinical setting which demonstrates benefit to patient outcomes in a chronic pain.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objectives of the study are to:

- 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.

8.2 SECONDARY OBJECTIVE:

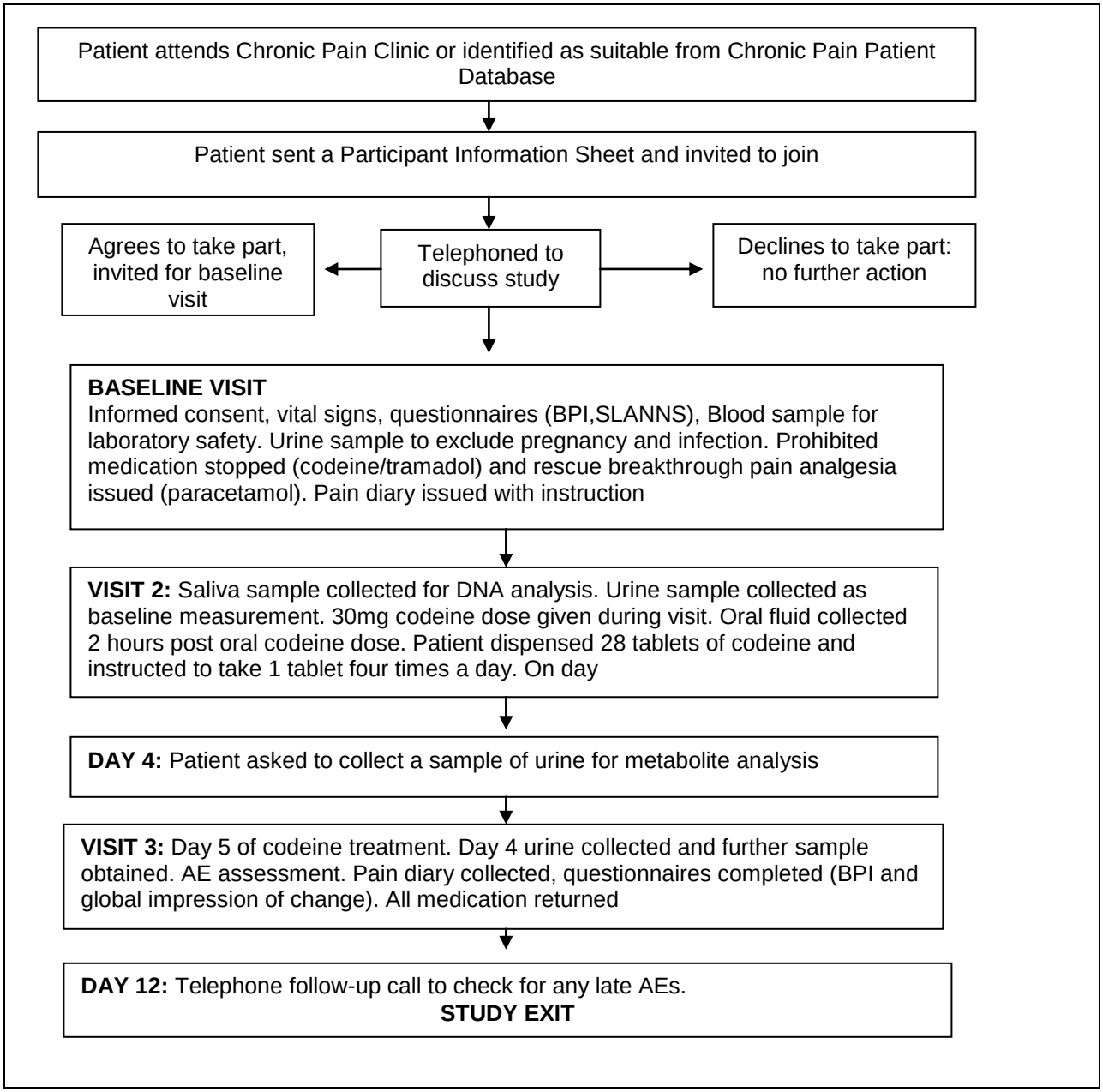
The secondary objectives of the study are to:

- Investigate whether codeine non-responsiveness is different in nociceptive, neuropathic and mixed pain states.
- Correlate genetic testing from saliva samples for CYP2D6 plus urine and oral fluid testing of morphine metabolites as predictors of codeine non-responsiveness.
- Investigate the pharmacogenetics of codeine phosphate and its implications in clinical practice for chronic pain clinic attendees.

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

Figure 1 Schematic Chart of Protocol



9.1.1 STUDY LOCATION

This study was conducted at the Pain Services Department, Seacroft Hospital Leeds.

9.2 DISCUSSION OF STUDY DESIGN

This single site, open label population study was developed using a clinical trial of a medicinal product (CTIMP) protocol. The protocol was peer reviewed by the research team at Seacroft Hospital and externally by two independent pain researchers not part of the Leeds Teaching Hospitals NHS Trust (LTHT). The statistical analysis was peer reviewed by an independent statistician at the University of Leeds. The final protocol was reviewed by the Research and Development plus the Quality Assurance team at LTHT before the study was granted sponsorship. The study was reviewed by approved by the Leeds East (Type 2, CTIMP flagged) Research Ethics Committee (REC) in addition to clinical trial authorisation from the Medicines and Healthcare Regulatory Agency (MHRA). The study was reviewed and adopted on to the UK Clinical Research Network portfolio part of the National Institute of Health Research (UKCRN, ID 7230) and registered on the international ISRCTN database (Trial identification number: 16874724).

9.3 SELECTION OF STUDY POPULATION

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. All potential participants had moderate pain suitable for WHO step 2 analgesics such as Codeine. Patient's whose pain was uncontrolled or escalating was excluded from inclusion. Potential study participants were identified from the current patient database held by pain services or directly from clinic by their pain consultant. Potential participants were contacted and invited to participate by post. Each potential participant received a letter of invitation, the REC approved patient information sheet and consent form approximately 14 days before the planned screening visit.

Potential participants were contacted by telephone the research nurse to discuss entry and elicit study suitability. Participants were invited to attend the pain research clinic at the hospital on three separate occasions and their participation in the study lasted no longer than 15 days. Willing participants were invited to attend a baseline visit (visit 1) at the pain clinic where they

were given ample time to make an informed decision as to whether to participate and to ask questions before signing the informed consent form. Informed consent was provided prior to any trial investigations being conducted. All stages of the consent process were clearly documented in the participant's medical notes, which clearly identified the participant was taking part in a clinical trial. Once informed consent had been given the participant was allocated a unique Identification number and their details recorded on a subject recruitment log stored in the Trial Master File (TMF).The participant's signed consent form, study information sheet (PIS), study data collection sheet and any correspondence to the participant or their GP in relation to the study were filed in the participants medical records.

9.3.1 INCLUSION CRITERIA

I. Male or female, Caucasian, aged between 18-80 years

II. Provided written informed consent

III. A persistent pain condition greater than 3 months duration that had been diagnosed by a pain management specialist

IV. Moderate to severe chronic pain (defined as a score of 4 (out of 10) or above on worst pain in the last 24 hours (question 3) on the Brief Pain Inventory at screening visit and daily as recorded in the pain diary during the wash out phase before visit 2)

V. Adequate renal function assessed as serum creatinine in females <130 mmol/l: and in males <150 mmol/l in a baseline blood sample at screening visit

VI. Liver enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT) less than twice the upper limit of normal and alkaline phosphates less than twice the upper limit of normal in a baseline blood sample at screening visit.

VII. Bilirubin within the normal range, or abnormalities clinically insignificant in the judgment of the investigator in a baseline blood sample at screening visit.

VIII. Deemed capable of complying with study schedule, procedures and medications.

9.3.2 EXCLUSION CRITERIA

I. Known sensitivity to codeine or participants who had a history of experiencing intolerable opioid analgesic side effects

II. Persistent pain which could be adequately controlled by increasing their dose of weak opioids

III. History of recreational drug or alcohol abuse use within the last 2 years

IV. Female participants who were pregnant, lactating or of child bearing potential who were not taking adequate contraceptive precautions i.e. an oral contraceptive, an approved hormonal implant, an intrauterine device or condoms/diaphragm and spermicide). A woman of childbearing potential was defined as any female who is less than 2 years post-menopausal or has not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral oophorectomy

V. Abnormal serum electrolytes or urine analysis, which in the medical investigator's opinion (Dr Karen Simpson (KS)) would exclude the participant from this study

VI. Haemoglobin level outside normal limits and white blood cell count below the lower limit of normal or above 12 x 109/l in a baseline blood sample at screening visit

VII. Participants who were receiving concurrent surgery, radiotherapy, chemotherapy or nerve blocks and those who received these treatments 4 weeks prior to commencing the study

VIII. Currently taking drugs known to be CYP2D6 inhibitors or that would interfere with the urinalysis e.g. morphine and were unable to cease taking their medication for the study period (Appendix 14.6)

IX. Anxiety or depression of a degree which in the medical investigator's opinion would exclude the participant from this study

X. Unable to understand and complete assessment questionnaires in English.

XI. Participated in another clinical study within the last 4 weeks

9.3.3 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences. The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be to be detrimental to the well-being of the patient. Patients who withdrew or were withdrawn underwent a final evaluation at visit 3. Patients who did not complete 5 full days of codeine treatment were replaced as part of the study design.

Full documentation was made of any withdrawals that occurred during the study in the data collection sheet and Trial Master File. The Investigator documented the date and time of the

withdrawal and results of any assessments made at this time. If the patient withdrew because of an adverse event (AE) or a serious adverse event (SAE) then details were forwarded to the Ethics committee as required. The investigator also forwarded details to LTHT (Sponsor) who forwarded details to the regulatory authorities as appropriate.

9.4 TREATMENTS

9.4.1 TREATMENTS ADMINISTERED

Participants were dispensed 64 Paracetamol tablets (500mg) as breakthrough analgesia at the baseline visit (visit 1, NIMP). The patient was instructed to take 1000mg 4-6 hourly (maximum of 4g in 24 hours) if their pain becomes unacceptable to them during this period and to record the amount, date and time breakthrough analgesia in their patient diary. At visit 2 participants received 28 tablets of 30mg Codeine Phosphate (IMP) in a blister pack to be taken orally. The patient was instructed to take 30mg (1 tablet) every 4 hours (up to a maximum of 120mg in 24 hours). Extra tablets (eight) were also provided in the blister pack in case of loss.

9.4.2 DESCRIPTION OF INVESTIGATIONAL PRODUCTS

Codeine Phosphate is a mu-opioid receptor analgesic, but is classed as a prodrug, reliant on bio-transformation by CYP2D6 to its active metabolites for analgesic effect. Codeine is glucuronidated, N- and O-Demethylated in phase-1 metabolism by enzymes UGT2B7, CYP3A4 and CYP2D6. N-Demethylation catalysed by CYP3A4 forms the metabolite norcodeine, which has no analgesic effect[28]. Approximately 10% of codeine is O-Demethylated by CYP2D6 to the analgesic active metabolite morphine but this can vary between individuals due to polymorphic variations in the enzyme which result from variations in the CYP2D6 gene[29]. The Codeine tablets 30mg were purchased by the LTHT Pharmacy Department from Phoenix H/C Distribution. They are manufactured by TEVA UK. Ltd and have a Manufacturers Authorisation (PL0289/506IR).

9.4.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Patients were enrolled in sequential order i.e. 01, 02, 03 etc. Each patient received Codeine at 30mg every four hours for 5 days.

9.4.4 SELECTION OF DOSES IN THE STUDY

Standard clinical doses of Paracetamol (1g as needed, up to 4g in 24 hours) and Codeine 30mg 4-6 hourly (maximum 240mg in 24 hours) were prescribed.

9.4.5 SELECTION AND TIMING OF DOSE FOR INDIVIDUAL PATIENTS

Patients were instructed to take Codeine four times a day 4-6 hours between doses. Patients were instructed to take 1g of Paracetamol for breakthrough pain as required during the study period but not to exceed 4g in 24 hours.

9.4.6 PRIOR AND CONCOMITANT THERAPY

Patients stopped all prohibited medications listed in Appendix 14.6 at the baseline visit (visit 1). Patients were allowed to continue with their prescribed antidepressant, anticonvulsant or non-steroidal anti-inflammatory (NSAID) medication providing the treatment was initiated at least 2 weeks prior to commencing the study, does not induce or inhibit the CYP2D6 enzyme and is at a stable dose. All concomitant medication and any changes therein were recorded in the data collection form (CRF: Appendix 14.7). Patients did not commence any new drug therapies throughout the Codeine treatment period.

9.4.7 TREATMENT COMPLIANCE

All study treatment was dispensed to the patient to be taken as instructed over the following 5 days. Patients were encouraged to return all used drug packaging and unused drugs at visit 3. Returned trial medication/packaging was returned to pharmacy for drug accountability and controlled destruction. All returned medication was counted and recorded on individual patient accountability records retained in pharmacy trial master file (TMF). Unused trial drug was destroyed by incineration by White Rose Environmental according to the LTH Trust Destruction Standard Operating Procedure.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 SAFETY MEASUREMENTS ASSESSED

9.5.1.1 VITAL SIGNS

Blood pressure and pulse was measured at each visit to monitor safety and to ensure there were no underlying medical conditions that require further investigation.

9.5.1.2 HAEMATOLOGY/SERUM CHEMISTRY

Maximum venous blood sample of 20 mls were collected at the baseline visit (visit 1) for clinical chemistry and haematology (to include electrolytes, serum creatinine, AST/ALT, alkaline phosphatase, bilirubin, haemoglobin, white blood cell count). This was done in accordance with the Leeds Teaching Hospital NHS Trust policy and practice guidelines. These baseline investigations were conducted to ensure there were no underlying medical conditions that require further investigation.

9.5.1.3 URINALYSIS

A urine sample was collected in a plain sterile container for dipstick urine analysis for PH, specific gravity, leukocytes, nitrates, protein, glucose, ketones, urobilinogen, billrubin and blood using Combur Test® reactive strips. These baseline investigations were conducted to ensure there were no underlying medical conditions that require further investigation.

9.5.1.4 PREGNANCY

Female patients of childbearing potential were required to have a negative urine pregnancy test as part of the inclusion criteria.

9.5.2 EFFICACY MEASUREMENTS ASSESSED

9.5.1.5 URINALYSIS FOR CODEINE O-DEMETHYLATION

A baseline urine sample was obtained for analysis of urinary codeine O-Demethylation metabolites at visit 2. The results of this baseline analysis were expected to be negative confirming no Codeine had been consumed during the analgesic wash out phase. On day four of the treatment period, participants were instructed to collect a sample of urine in a universal container supplied at visit 2 and store in a cool location until they returned to clinic the following

day for the end of study visit. This was to allow analysis of urinary codeine O-Demethylation metabolites concentrations at a time when the participant is well equilibrated with Codeine. A final urine sample was collected at the end of study (visit 3). Urine samples were collected in sterile universal containers identifiable by the participant's trial number, initials, date of sample and stored within the pain clinic at Seacroft Hospital at -20^{o}C. Samples were transported in batches to the LTHT laboratories and analysed according to ICH good laboratory practice (GLP) using an automated validated bio-analytical assay incorporating liquid chromatography with tandem mass spectroscopy (LC-MS/MS). The standard lower limit of quantification (LLQ) for Codeine metabolites using this technique is 10ng/ml, with the higher limit of quantification (HLQ) reported as >500ng/ml (standard NHS practice).

9.5.1.6 ORAL FLUID SAMPLE

Oral fluid collection for opiate analysis provides comparable results to urine testing and is a reliable matrix for opiate detection[30]. Oral fluid is the collective term used for all the secretions found in the mouth. These include saliva, oral mucosal transudate, bacteria, mucroproteins, enzymes, cells, electrolytes and food debris. The analysis is centred on the OMT which is also known as gingival crevicular fluid and comes from the area between the teeth and the gums which is virtually impossible to collect on its own. Over the last 5 years oral fluid has increasingly been widely used as a specimen in pharmacokinetic studies, therapeutic drug monitoring and for the detection of illicit drugs.

The collection of oral fluid is simple, painless and non-invasive to the participant. Two hours post codeine dose participants were asked to provide an oral fluid sample. Oral fluid was collected using the Intercept® collection pad. Participants were instructed to place the collection pad between the lower cheek and gums and gently rub back and forth along the gum line until the pad was moist. Once the pad was moist it was left in the mouth for 2 minutes, following which it was removed and placed into a specimen vial containing 15% methanol in 4ml Ammonium Acetate. The oral fluid samples were frozen and stored at -20^{o}C. Samples were transported in batches and analysed at the LTHT laboratories for free codeine, morphine, norcodeine and glucuronides of morphine and codeine. This procedure was only completed in 20 participants and was removed from the study protocol by substantial amendment following interim analysis which failed to detected codeine metabolites in oral fluid.

9.5.1.7 CYP2D6 GENOTYPING

Following a 30 minute oral fast a 2ml saliva sample was collected for CYP2D6 genotyping using the non-invasive Oragene•DNA Self-Collection Kit. The kit is an all-in-one system for the collection, preservation, transportation and purification of DNA from saliva. Samples were coded with the participant's trial number, initials, date of sample and stored in a secure dry place, protected from light at room temperature within the pain clinic. Samples were transported ambient in batches to KBiosciences Laboratory, Hertfordshire UK for DNA extraction and processing. CYP2D6 allele selection and base sequencing for identification was determined from allele frequencies for a Caucasian population from the literature[6,8,10,11,13-17] represented in Appendix 14.8. The samples underwent DNA extraction and processed by KASP™ (competitive allele specific polymerase chain reaction) for CYP2D6 alleles *1,*2,*3,*4,*5,*6, *9, *10, *41 and Hybeacon assay for CYP2D6 duplication. Identified alleles were allocated a CYP2D6 activity score using Gaedigk et al., (1999)[31] scoring method. Phenotype was inferred from the total activity score of both alleles and duplications using Crews et al. (2012)[32] classifications (Appendix 14.8).

9.5.1.8 DAILY PAIN SCORES RECORDED IN THE PARTICIPANT'S DIARY

The pain diary was issued to patients at visit 1 with the instruction to complete daily before retiring to bed. The diary consisted of the Brief Pain Inventory (BPI) a validated pain questionnaire that measures pain severity and pain interference on activities of daily living. The diary also included prompt questions to record any adverse events and any breakthrough analgesia used.

The definition of a codeine non-responder used as a primary endpoint in this study was a participant who did not display a mean 30% reduction in day 0-day4 average pain recorded on a 0-10 NRS scale compared to baseline average pain score following codeine therapy 30mgs QDS.

Table 3 shows the schedule of examinations and procedures.

Procedures	Baseline Visit (+/-1day)	Visit 2 (+/-1day)	At home	Visit 3 (+/-1day)	Follow up (+/-1day)
	Day -2	Day 0	Day 4	Day 5	Via Telephone day 12
Informed Consent	x				
Vital signs	x	x		x	
Pain Questionnaires: m-BPI-sf and SF-8	x	x		x	
SLANSS	x				
Lab Safety Tests	x				
Global impression of change				x	
Recording AE's		x	x	x	x
Saliva sample for genetic testing		x			
Oral fluid sample 2 hours post codeine dose		x			
Urine sample for opioid metabolites		x	x	x	
Urine sample for dipstick analysis and pregnancy testing for females	x				
Patient pain diary dispensed	x	x			
Prohibited medication ceased	x				
Breakthrough analgesia: Paracetamol prescribed 1g 4-6 hourly	x				
Study medication dispensed: Oral Codeine30 mg 4 hourly		x			

9.6 DATA QUALITY ASSURANCE

The study was regularly monitored by the sponsor and reports issued are filed in the TMF. The Sponsor had systems in place to ensure there was reporting and appropriate action taken in respect of serious breaches of GCP, the trial protocol and/or the Clinical Trial Authorisation. A "serious breach" was classed as a breach which was likely to effect to a significant degree the safety or physical or mental integrity of the participants of the trial; or the scientific value of the trial. The Investigator promptly notified the Sponsor QA Office of the following within the required timeframe, once they become aware of:

(a) Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation (none during study).

(b) Urgent safety measures (none during study)

(c) Protocol violations (6 reported during study period relating to missed doses of codeine by patients during the study period. All violations have been recorded in the TMF).
(d) Any amendments to the trial (three in total)
(e) Any changes the Clinical Trial Risk Assessment (Form A; none).
(f) Any other issues as stated in the Research Sponsorship Agreement (RSA: none)

9.7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

9.7.1 STATISTICAL AND ANALYTICAL PLANS

The primary endpoint was the participant's status as a codeine responder or non-responder. The overall proportions of codeine responders were estimated and 95% confidence intervals were produced using the exact binomial distribution. The responder/non-responder status was tabulated against the four genetic groups. Logistic regression was used to formally compare the proportions.

The log-transformed levels of urinary morphine metabolites measured in urinalysis were summarised for responders and non-responders, the four genetic groups and oral fluid using means, standard deviations, medians and range using box-and-whisker plots. ANOVA were used on urinary morphine metabolites to compare the four genetic groups.
Logistic regression was used with the log-transformed levels urinary morphine metabolites as covariates to predict the responder/non-responder status. A multivariate logistic regression model that combined the genetic group and the log-transformed urinary morphine metabolites levels to predict responder/non-responder status was fitted. The suitability of the model as predictor of responder/non-responder status was assessed using ROC curves.

The secondary endpoints, BPI, SLANSS and Global Impression of Change, were summarised by responder/non-responder status and by genetic group in terms of means, standard deviations, median and range.

The subject population for analysis was defined as follows:
• Enrolled population: Any subject who attended the screening visit.
• Intention to Treat (ITT) population: Any subject who attend three visits and thus had their genetic group determined and the primary endpoint was observed.

9.7.2 DETERMINATION OF SAMPLE SIZE

A sample size of 121 subjects will give 90% power to detect a larger proportion of codeine non-responders than the null hypothesis of 10%, assuming the true proportion is 20%, using a 5% significance level for a 1-sided test.

A drop-out rate of 20% was assumed thus implying recruiting 150 subjects would give 121 evaluable subjects.

9.7.3 PROTOCOL AMENDMENTS

During the study three substantial amendments were approved as follows:

Table 4: Protocol amendments during study period

Date of Amendment	Amendment Details	Rationale
12th Feb 2010	Addition of poster advert, no change to protocol	Approved poster placed in Pain Clinics to aid study awareness and improve study accrual
8th 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.
14th August 2012	Change to inclusion criteria number V from: Patients with moderate to severe chronic pain (defined as a minimum of 40 mm pain score on the 100mm pain visual analogue scale (VAS) at screening and a minimum average daily pain score of 4 on Daily Pain Rating Scale (DPRS) during pre-treatment. To: Patients with moderate to severe chronic pain (defined as a score of 4 (out of 10) or above on worst pain in the last 24 hours (question 3) on the Brief Pain Inventory at screening and daily in the Patient Diary during pre-treatment.)	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.

9.8 STUDY POPULATION

Figure 2: DISPOSITION OF PATIENTS

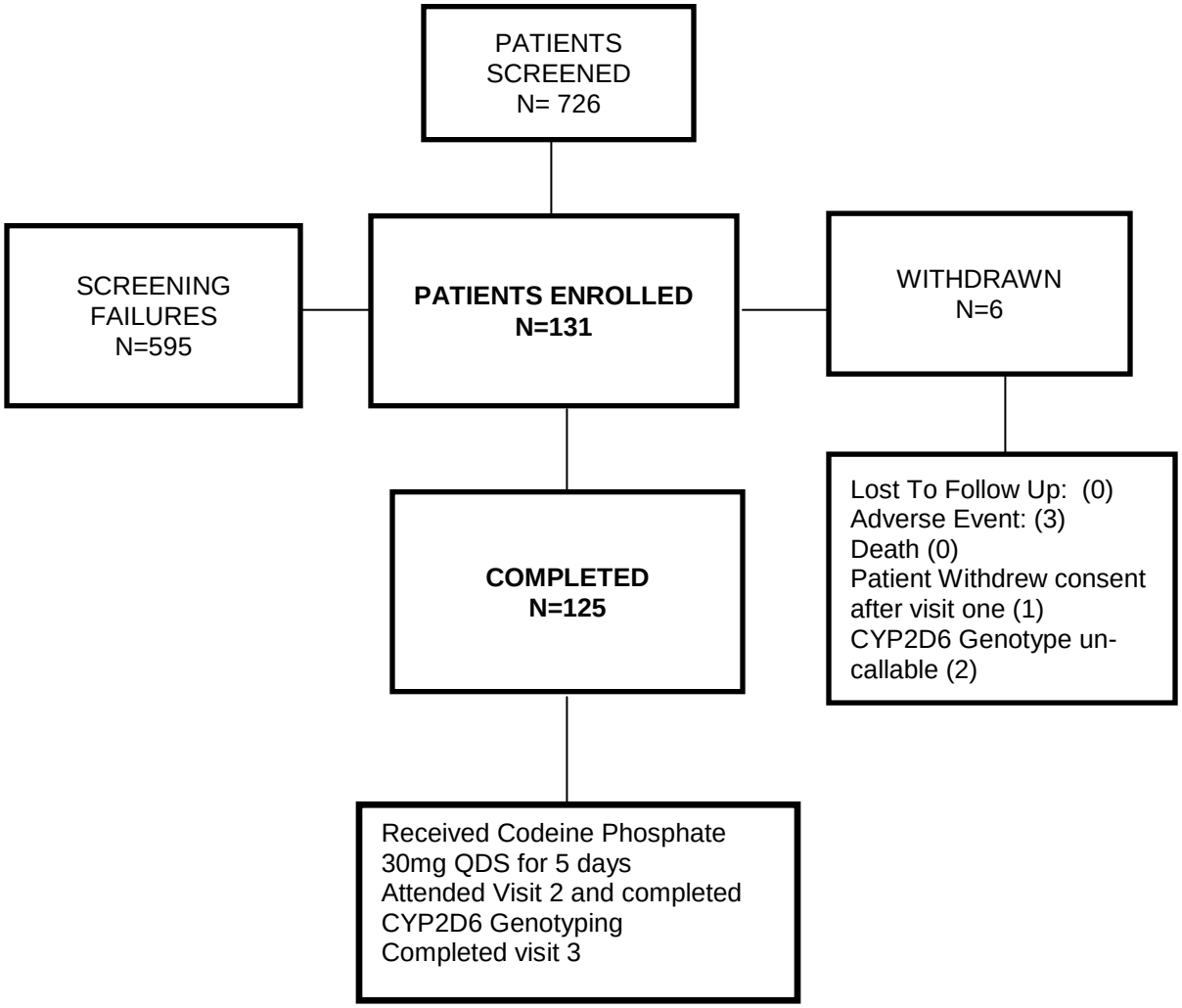


Table 1: Disposition of patients

	Sample Group (N=131)
Enrolled	131
Completed visit 1	131
Completed visit 2	130
CYP2D6 Genotyping confirmed	128
Completed visit 3	125
Withdrawn:	
Lost to follow up	0
Adverse event	3
Death	0
Other	3

9.9 PROTOCOL DEVIATIONS

Table 2 gives details of study protocol deviations.

Table 2 Protocol deviations

Deviation	*Site: Seacroft Leeds*
Entry criteria	1
Withdrawal criteria	0
Incorrect dosing regimen	4
Concomitant treatment/medication	0
Other	4

9.10 RESULTS

9.10.1 DATA SETS ANALYSED

A total of 131 participants were enrolled into the study from October 2009 to June 2014 (enrolled population). The enrolled population consisted of 52 males, aged 27-78 years and 79 females, aged 23-79 years (Table 3). The enrolled population contained 20.62% more females than males. The intention to treat population (ITT) included 125 participants, with 51 males aged 27-78 years and 74 females aged 23-77 years (Table 3). The ITT sample contained 18.4% more females than males; however both groups were well matched in age range and mean.

9.10.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 3 Demographics of the Study Patients

	Enrolled Group (n=131)			ITT Group (n=125)		
	Male	Female	Total	Male	Female	Total
Number (%)	52 (39.7)	79 (60.3)	131 (100)	51 (40.8)	74 (59.2)	125 (100)
Age range	27-78 years	23-79 years	23-79 years	27-78 years	23-77 years	23-79 years
Age mean ±SD	57.00 ±12.23	55.63 ±14.91	56.17 ±13.88	57.10 ±12.33	55.64 ±14.74	56.26 ±13.71

9.10.3 DISTRIBUTION OF NEUROPATHIC AND NOCICEPTIVE PAIN STATE

Analysis of the S-LANSS pain questionnaire to determine the participant's pain state was conducted for both the enrolled population and the ITT population. Nociceptive pain was more prevalent for both sexes than neuropathic pain reported by 58.02% of the enrolled population (Section 12, Table 4). Nociceptive pain was reported more in male participants compared to females (Section 12, Table 4). A higher proportion of females reported neuropathic pain when compared to males (Section 12, Table 4).

9.10.4 ANALGESICS AND PAIN ADJUVANTS PRESCRIBED AT STUDY ENTRY

In the enrolled group 4.58% of the sample were not taking any prescribed or over the counter analgesics or pain adjuvants. One analgesic or pain adjuvant was the commonest prescribing trend in 27.48% of the enrolled population. In line with national guidelines the majority of the participants were receiving more than one analgesic or pain adjuvant. In combination therapy approaches, two analgesics and or pain adjuvants were the commonest trend prescribed to 25.19% of the enrolled population. This was closely followed by three analgesics and or pain adjuvants (22.9%) and four analgesics and or pain adjuvants drug combinations (16.03%). Few participants were prescribed five analgesics/pain adjuvants drug combinations (1.53%) or six analgesics/pain adjuvants drug combinations (2.29%). Section 12, Table 5 reports a summary of prescribed analgesics and pain adjuvants prior to commencing study for the enrolled group.

9.10.5 CYP2D6 ANALGESIC PRODRUGS PRESCRIBED PRIOR TO STUDY ENTRY

CYP2D6 analgesic prodrugs were prescribed to 58.79% of the enrolled population at study entry (Section 12, Table 6). Co-codamol (Codeine and Paracetamol combined) was the most common CYP2D6 prodrug prescribed to 23.66% of the participants at study entry. Frequency of co-codamol prescriptions was higher in females (25.32%) when compared to males (21.15%). Tramadol was the second commonest CYP2D6 prodrug prescribed to 19.85% of the sample, with a higher frequency in females (21.52%) compared to males (17.31%). Codeine phosphate was prescribed to 11.45% of the sample with similar proportions within females (11.39%) compared to males (11.54%). Only 3.82% of the participants were prescribed two concurrent CYP2D6 prodrug analgesics with a higher frequency in males (2.29%) when compared to females (1.53%), the commonest combination of CYP2D6 prodrugs were codeine + tramadol (1.53%) and co-codamol + tramadol (1.53%).

9.10.6 CYP2D6 ANALGESIC PRODRUGS PREVIOUSLY TRIED PRIOR TO STUDY ENTRY

69.47% of the enrolled population reported that they failed to respond to one or more CYP2D6 analgesic prodrugs prescribed for persistent pain. Tramadol was the most common prodrug, previously tried by 38.17% of the enrolled population with similar proportions in both sexes (Section 12, Table 7a). Co-codamol was the second commonest prodrug, previously tried in 35.11% of the enrolled population with similar proportions in both sexes. Codeine was previously tried by 21.37% of the enrolled population, with higher frequency in males (26.92%) when compared to females (17.72%).

18.33% of the enrolled population reported that they failed to respond to two CYP2D6 prodrugs (Section 12, Table 7b). 10.69% of the enrolled population reported that they failed to respond to tramadol and co-codamol; with higher frequency in females (12.66%) when compared to males (7.69%). 3.05% of the enrolled population reported that they failed to respond to all three analgesic prodrugs with a higher frequency in males (5.77%) when compared to females (1.27%).

9.10.7 ANALGESIC RESPONSE TO FIVE DAYS CODEINE PHOSPHATE 30MG QDS

Two out of the 131 saliva samples collected for CYP2D6 genotyping were discarded. In one sample, allele duplication indicating the UM phenotype if present or EM phenotype if absent was

unable to be determined. In the other sample, the reduced function allele *41 presence was not determined. Decision to discard these samples from analysis is based on the CYP2D6 activity score could not be confirmed and phenotype could not be confidently inferred.

From the enrolled population of 129 participants, 9.3% were PMs with a higher proportion of females (10.39%) when compared to males (7.69%). The proportion of PMs within this study sample is comparable to the 5-10% reported in a general Caucasian population. Only 4.65% of the sample was CYP2D6 IMs which is considerably lower than 10-15% reported in a general Caucasian population (Section 12, Table 8). However 9.62% males were CYP2D6 IMs which is comparable to the reported prevalence in a general Caucasian population compared to only 1.30% females which is considerably lower than the expected proportion.

The EM phenotype is inferred to activity scores 1, 1.5 and 2 for this study. As expected the majority of the EM phenotype group possessed full CYP2D6 activity, AS 2 (45.74%). The second largest frequency was EM AS 1 at 24.81% which is higher than EM AS 1.5 at 13.95%. EM phenotypes therefore represented 84.5% of the sample, which is higher than expected compared to 70-80% reported in a general population. UMs AS >2 were lower than expected with 1.55% compared to 5.5% seen in a general population.

The frequency of *CYP2D6* diplotypes observed in the enrolled sample (n=129) is reported in Section 12, Table 9. The most common diplotype observed was *CYP2D6**1/*2 (EM AS 2), closely followed by the wild type CYP2D6*1/*1 (EM AS 2). CYP2D6*1/*4 (EM AS 1) was the third commonest genotype and CYP2D6*4xN/*4 (PM AS 0) was the most common genotype for the PM phenotype.

When genetically inferred CYP2D6 phenotype is compared to the participants current prescribed analgesic medication (Section 12, Table 10), 11.63% were prescribed CYP2D6 prodrugs yet have CYP2D6 polymorphisms resulting in PM, IM or UM phenotypes with the likelihood of suboptimal analgesic response. When compared to previously tried prodrug analgesic medication (Section 12, Table 11), only 10% included PM, IM and UM phenotypes whereas 32% of EMs AS 2 reported failure to respond.

9.10.8 ANALGESIC RESPONSE TO FIVE DAYS CODEINE PHOSPHATE 30MG QDS

Pain scores were recorded by the participants using the m-BPI-sf throughout the study in the ITT population (n=125). “Average pain” in the last 24 hours was recorded on a 0-10 point numerical rating scale (NRS) at baseline visit and each evening from commencing codeine treatment (day 0) to completing the study (day 5). Mean “average pain” scores were calculated with standard deviation and range at baseline (6.31 ± 1.76, range 2-10, median 6) and from day0-day4 (5.66 ± 2.11, range 1-10, median 5.8) (Section 12, Table 12a-12b). There was a significant reduction at the p<.05 level in mean “average pain” scores recorded at baseline compared day0-day4 observed in males (two sample t-test, p=0.003) (Section 12, Table 13a) and females (two sample t-test, p=0.0003) (Section 12, Table 13b).

The pain severity score was calculated as the mean value of the total sum of NRS scores for “worst”, “least”, “average” and “current” pain within the last 24 hours. Mean pain severity scores were calculated with standard deviation and range at baseline (6.09 ± 1.75, range 1.5-10, median 6.) and from day0-day4 (5.67 ± 2.17, range 0.85-10, median 5.7, Section 12, Table 14a-14b). There was a significant reduction at the p<.05 level in mean pain severity scores recorded at baseline compared day0-day4 observed in males (two sample t-test, p=0.048. Section 12, Table 15a) and females (two sample t-test, p=0.0074. Section 12, Table 15b).

The pain interference score indicates the impact of pain on seven activities of daily living in the previous 24 hours. Participants were asked to rate how much their pain interfered with general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life on a 0-10 NRS scale. The pain interference score was calculated as the mean value of the total sum of the seven aspects of daily living. Mean pain interference scores were calculated with standard deviation and range at baseline (6.14 ± 2.11, range 0.1-10, median 6.29, Section 12, Table 16a) and from day0-day4 (5.02 ± 2.51, range 0.39-9.97 and median 4.8. Section 12, Table 16b). There was a significant reduction at the p<.05 level in mean pain severity scores recorded at baseline compared day0-day4 observed in males (two sample t-test, p=4.64E-06. Section 12, Table 17a) and females (two sample t-test, p=3.75E-09. Section 12, Table 17b).

Analgesic response was calculated as a ≥30% reduction of the mean day0-day4 “average pain” in 24 hours measured on a 0-10 NRS scale compared to baseline. Participants reaching this marker at the end of the codeine therapy were defined as codeine responders. 19.61% of males were categorised as codeine responders compared to 21.62% of females. In the codeine

responders group the mean reduction in pain scores were 49% in males compared to 47% in females (Section 12, Table 18).

Comparing codeine analgesic response to CYP2D6 phenotype, 100% of PMs, IMs and UMs were categorised as codeine non-responders. When the CYP2D6 activity scores are compared in the EM phenotype an increasing trend is observed in males and females reporting codeine non-response correlating to level of CYP2D6 enzyme function they possess (Section 12, Table 19a, Table 19b). Nearly 70% of EMs with two fully functionally alleles (AS 2) reported codeine non-response compared to nearly 78% EMs AS 1.5 and 84% EMs with one fully functional or two partially functional alleles ((Section 12, Table 19a, Table 19b).

CYP2D6 PM, IM and UM phenotypes were all negatively binomial distributed suggesting that these phenotypes would not respond to codeine in the general population. Codeine response between EM phenotypes with differing activity scores varied from 16% for AS 1, 22% for AS 1.5 and 30% for AS 2 with positively skewed binominal distribution. Using exact binominal distribution, codeine response within the EM phenotype can be estimated at 3% to 28% for EM (AS 1), 2% to 42% for EM (AS 1.5) and 18% to 43% for EM (AS 2) with a 95% confidence interval (Section 12, Table 20). Thus rejecting the null hypothesis of the proportion of codeine non-responders represents 10% in a persistent pain population. When comparing the proportion of codeine responders (defined by ≥30% reduction in “average pain” NRS score from day0-day4 of codeine 30mg QDS when compared to baseline) within the EM phenotype, there is a clear difference in relation to the CYP2D6 activity score. Figure 3 (Section 12) demonstrates differing codeine responders percentages within the EM phenotype that increases in line with each increase in activity score.

Logistic regression analysis was used to estimate the effect of CYP2D6 activity score on codeine response (defined by ≥30% reduction in “average pain” NRS score from day0-day4 of codeine 30mg QDS when compared to baseline). The dependent variable which measures codeine response is discrete (yes=1, no=0) with CYP2D6 activity score as the independent variable. Results indicate that codeine response increases with CYP2D6 activity score (Section 12, Table 21). The coefficient on the CYP2D6 activity score has a Wald statistic equal to 5.67 which is significant at the 0.017 level (95% confidence interval). The model Chi-square was significant at 0.009 indicating that CYP2D6 activity score affect codeine response (value=6.78, df=1, p=0.009, CI: 95%). The ‘odds ratio’ for CYP2D6 activity score coefficient is 2.62 with a 95% confidence interval (1.186-5.790). This suggests that individuals with high CYP2D6 activity

score are 2 times more likely to respond to codeine than individuals with a low CYP2D6 activity score.

9.10.9 ANALYSIS OF O-DEMETHYLATION CODEINE METABOLITES IN ORAL FLUID

Analysis of oral fluid collected two hours post 30mg oral codeine dose in 20 samples identified one participant (5%) as positive for codeine metabolites. Following discussions with Dr Fox (laboratory investigator) it was concluded this method was unsuitable to be used as a method of inferring CYP2D6 phenotype post codeine dosing. No further analysis was conducted and oral fluid sampling was removed from the study design by substantial amendment two. .

9.10.10 ANALYSIS OF URINARY O-DEMETHYLATION CODEINE METABOLITES

One out of the 125 day 4 urine samples collected for analysis of urinary codeine O-Demethylation metabolites was discarded due to leaking in transit from clinic to the laboratory. The urine samples were analysed for urinary total morphine (ng/L) and reported for each phenotype and activity score according to codeine responder status (Section 12, Table 22). Within the codeine responder EM phenotypes an increasing trend in detectable total morphine metabolites was observed as CYP2D6 activity level increased.

The urinary total morphine metabolites were log transformed to reduce skew using a base-10 logarithm (geometric mean of the raw data is 10, arithmetic mean of the log transformed value is 1). One PM day 4 urine sample was negative for urinary total morphine metabolites (0ng/L) and therefore was not included in the log transformed calculations. Log transformed data was categorised to responder status and CYP2D6 phenotype and plotted on box and whisker charts (Section 12, Fig 4a and Fig 4b). Codeine non-responders phenotypes PM (n=10), IM (n=6), EM AS 1.5 (14) and UM (n=2) all contained less than the recommended minimum of 20 data sets for this analysis process and therefore may be misleading. Likewise in the codeine responder phenotypes EM AS 1 (n=5), EM AS 1.5 (n=4) and EM AS 2 (n=17) sample numbers are too small and cannot be confidently interpreted using box and whisker plots. Therefore an individual value plots (recommended for sample sizes ≤50) were used for codeine non-responders and codeine responders to observe the distribution spread using raw urinary total morphine metabolite data (Section 12, Fig 5a and Fig 5b). The codeine non-responders urinary total morphine metabolite data showed as expected low metabolite concentrations for PM and

IM phenotypes. When the urinary total morphine metabolites are compared between codeine responders and non-responders in the EM phenotype (AS 1, AS 1.5 and AS 2) there is no difference in distribution. However this may be due the small sample sizes in the codeine responder compared to the codeine non responder group.

Urine samples were analysed for creatinine levels in an attempt to correct samples for levels of hydration. By dividing the urinary total morphine by the creatinine concentration (morphine:creatinine ratio) a more accurate level of urinary total morphine metabolites was obtained (Section 12, Table 23). Individual value plots were also used for raw urinary morphine:creatinine ratio data in the codeine non-responders and codeine responders for comparison of distribution spread (Section 12, Fig 6a and Fig 6b). The morphine:creatinine ratio distribution spread is similar to total morphine, however there is no difference in distribution between the EM codeine responders and non-responders which may be due the small sample sizes in the codeine responder group.

A one way ANOVA was conducted to compare the effect of CYP2D6 activity score on the log transformed urinary total morphine (Section 12, Table 24) and morphine:creatinine ratio (Section 12, Table 25) following four days of oral codeine 30mg QDS. There was a highly significant effect of increase in CYP2D6 activity score on log transformed urinary total morphine metabolites (Section 12, Table 24) and morphine:creatinine ratio (Section 12, Table 25) at the $p<.05$ level for all six levels of CYP2D6 activity. A further one way ANOVA analysis was conducted to compare responder status on the log transformed urinary total morphine metabolites and morphine:creatinine ratio in the EM phenotype (AS 1, AS 1.5 and AS 2) which were not significance at $p=0.05$ level which again may be due to the small codeine responder sample sizes.

No statistical significance was observed in the logistic regression analysis, using log transformed urinary total morphine metabolites and log transformed morphine:creatinine ratio as covariates to predict codeine response (defined as ≥30% reduction in average pain score from day 0-day4 of codeine 30mg QDS when compared to baseline. Table 5.12). No statistical significance was observed using a multivariate logistic regression model combining the CYP2D6 phenotype activity scores, the log transformed urinary total morphine metabolites and log transformed morphine:creatinine ratio as covariates to predict codeine response (defined as ≥30% reduction in average pain score from day 0 - day 5 of codeine 30mg QDS when compared to baseline).

9.10.11 CODEINE URINARY METABOLITE PREDICTION MODELS

Using mean day 4 urinary total morphine metabolite concentrations and mean day 4 morphine:creatinine ratio for each CYP2D6 phenotype activity score and codeine responder status a novel model and scoring system for predicting CYP2D6 activity score was developed (Section 12, Table 25 (model 1) and Table 26 (model 2)). No statistical significance was observed with either model in logistic regression using day 4 urinary total morphine metabolite or total morphine:creatinine ratio concentrations as a method to infer CYP2D6 activity score.

Two further novel models and scoring systems were developed to predict codeine responder status instead of CYP2D6 activity score. Using mean day 4 urinary total morphine metabolite concentrations and mean day 4 morphine:creatinine ratio as guide predictors for codeine response or non-response, a range of metabolite concentrations and expected response to codeine was developed (Section 12, Table 27 (model 3) and Table 28 (model 4).

A logistic regression analysis was conducted to predict codeine response using the model 3, day 4 urinary total morphine metabolite concentrations as predictors. A test of the full model against a constant only model was significant at the $p<.05$ level for predicting codeine responder status (i.e. codeine responder: expected ≥30% reduction in average pain score from day0-day4 of codeine 30mg QDS when compared to baseline. Section 12, Table 29). The model Chi-square goodness of fit was highly significant (value=43.47278, df=1, p= 4.3E-11, CI: 95%). Prediction success overall was 79% (82% for expected codeine non-responder, 75% for expected codeine responder) with sensitivity 0.8 and specificity 0.78 (Section 12, Fig 7).

A logistic regression analysis was conducted to predict codeine response using the model 4, day 4 urinary total morphine:creatinine ratio metabolite concentrations as predictors. A test of the full model against a constant only model was significant at the $p<.05$ level for predicting codeine responder status (i.e. codeine responder: ≥30% reduction in average pain score from day0-day4 of codeine 30mg QDS when compared to baseline. Section 12, Table 30). The model Chi-square goodness of fit highly significant (value=44.46494, df=1, p= 2.59E-11, CI: 95%). Prediction success overall was 79% (88% expected codeine non-responder, 68% expected codeine responder) with sensitivity 0.76 and specificity 0.83 (Section 12, Table 30 and Fig 8).

9.10.11 ANALYSIS OF CYP2D6 AUTOPHENOCOPYING

Participant's concurrent medication was analysed to determine if the number of CYP2D6 substrates impacted on codeine response through autophenocopying. CYP2D6 substrate classification was determined through bioinformatics and cheminformatics databases[33-34] for each drug identified. Study medication (Codeine 30mg QDS and Paracetamol 1g PRN) was excluded from the analysis. Number of substrates was tabulated against CYP2D6 phenotype and codeine response status (Section 12, Table 31). In logistic regression analysis no significance was found in the number of concurrent CYP2D6 substrates, urinary morphine metabolites and codeine response status.

9.10.12 ANALYSIS OF PARTICIPANTS GLOBAL IMPRESSION OF CHANGE AND CLINICIANS GLOBAL IMPRESSION OF CHANGE

Participants were asked to rate their health state at the end of study (day 5) compared to baseline using a Global Impression of Change (PGIC) 7 point scale of "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse" and "very much worse". As expected the majority of CYP2D6 PM participants reported no change or a negative effect. The majority of IM participants reported improvement even though no analgesic efficacy was obtained through codeine therapy. The majority of EM (AS 1) codeine non-responders reported a reported "no change" or a negative effect with codeine therapy. Whereas EM (AS 1) codeine responders reported "no change" when compared to baseline. One EM (AS 1.5) codeine non-responder reported "very much improved" without analgesic efficacy with the majority reporting "no change". EM (AS 1.5) codeine responders reported either "no change" or "minimally improved". The majority of EM (AS 2) codeine responders reported "minimally" to "much improved" with one participant reporting "very much worse" who reached >30% reduction in "average pain" scores during the study period. Five EM (AS 2) codeine non-responders reported improvements compared to baseline, with the majority reporting no change (Section 12, Table 31).

The Clinicians Global Impression of Change (CGIC) was completed by the Research Nurse at the end of study visit (Day 5) using the same scale as the PGPC. The CGIC was completed after reviewing the participant's pain diary and any adverse events reported during the visit. The CGIC was compared to the self-reported PGIC for accuracy and was successfully matched in 72% of the participants (Section 12, Table 32).

9.11 MEASUREMENTS OF TREATMENT COMPLIANCE

Patients were encouraged to return all used drug packaging and unused drugs at visit 3. Returned trial medication/packaging was returned to pharmacy for drug accountability and controlled destruction. All returned medication was counted and recorded on individual patient accountability records retained in pharmacy trial master file (TMF). Unused trial drug was destroyed by incineration by White Rose Environmental according to the LTH Trust Destruction Standard Operating Procedure. Medication compliance ranged between 75-100%, with 82.4% of the participants fully compliant.

9.12 STUDY DURATION

The study commenced recruitment in October 2008 and closed to recruitment in June 2015 following enrolling 131 participants. The last participant last visit was completed on 30th June 2015.

9.13 STATISTICAL/ANALYTICAL ISSUES

9.13.1 WITHDRAWN ENROLLED PARTICIPANTS NOT INCLUDED IN THE ITT POPULATION

One male participant withdrew consent following the baseline visit without giving a reason. Two females CYP2D6 genotype could not be determined and did not respond to requests to provide a further sample for analysis. Three females withdrew from the study due to adverse events listed in Section 12, Table 33. The data collected for the withdrawn participants were included in the analysis of the enrolled group but not the analysis of the ITT group.

10 SAFETY EVALUATION

10.1 ADVERSE EVENTS (AE's)

There were no reported serious adverse events (death, life-threatening events, prolonged or requirement for hospitalisation) during the course of this study. Adverse events (defined as any untoward medical occurrence observed in a participant during or following administration of codeine which did not necessarily have a causal relationship with treatment) were self-reported

by the participants through the pain diary or verbally at study visits. Adverse events were separated into “expected” as documented on the Codeine Phosphate 30mg Summary of Product Characteristics (Appendix 14.9) and “unexpected” (not recorded in the SmPC). From the “expected” self-reported adverse events, headache was the most frequent at 37%, followed by nausea at 33% and constipation at 30% (Section 12, Table 34). Interestingly the majority of these adverse events were reported by codeine non-responders (< 30% reduction in mean average pain scores from day0-day4 when compared to baseline). From the “unexpected” self-reported adverse events diarrhoea was the most frequent at 10% followed by stomach cramps and flu like symptoms at 9% (Section 12, Table 35). Again the majority of these adverse events were reported by codeine non-responders. No statistical significance was observed in logistic regression analysis of CYP2D6 activity score, responder status and headache, constipation, dry mouth, nausea and drowsiness.

10.2 SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

No Serious adverse events were observed during the study period.

11 DISCUSSION AND OVERALL CONCLUSIONS

The main findings of this study are as follows:

- 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.
- The frequency of IM phenotypes in this sample is considerable smaller than expected in a general population
- Codeine response could be predicted with 79% accuracy using a novel prediction model scoring system based on urinary total morphine metabolites concentrations (model 3) and morphine:creatinine ratio from day 4 urine samples collected during day0-day5 oral codeine 30mg QDS for persistent pain.

Each of these findings will be discussed in turn.

11.1 THERAPEUTIC ANALGESIC RESPONSE TO CODEINE 30MG QDS

The study found therapeutic analgesic response to codeine 30mg QDS was lower than expected in CYP2D6 extensive metaboliser phenotypes. Participants who were categorised as PM (AS 0), IM (AS 0.5) and UM (AS >2) metabolisers accounted for 15.5% of the sample. As expected due to their CYP2D6 phenotype these participants did not display a ≥30% reduction in mean day0-day4 “average pain” in the last 24 hours scored on a 10 point NRS scale when compared to baseline and were defined as codeine non-responders.

The EM phenotype consisted of three enzyme activity scores of AS 1, AS 1.5 and AS 2 relating to level of function and accounted for 84.5% of the sample. The EM phenotype is classed as normal CYP2D6 function with the capacity to bio-transform codeine to its active metabolite morphine to provide therapeutic analgesic effect. Yet only 25% of CYP2D6 EM participants displayed a ≥30% reduction in mean day 0-day 5 “average pain” in the last 24 hours scored on a 10 point NRS scale when compared to baseline and defined as codeine responders. The low percentage of codeine responders in the EM phenotype was unexpected for several reasons. The participants were predominantly reporting persistent nociceptive pain recorded via the SLANSS validated questionnaire. Nociceptive pain and mixed pain states often respond to codeine therapy unlike neuropathic pain with requires combined therapy with a pain adjuvant for efficacy, therefore a higher response to codeine was expected in the EM phenotype.

Clinically failing to respond to at least one CYP2D6 prodrug previously was self-reported by 69.47% of the sample. Tramadol was the most common drug previously tried followed by co-codamol and to a lesser extent codeine. At study entry, 58.8% of the sample were currently prescribed a CYP2D6 prodrug analgesic, predominantly co-codamol and tramadol for their persistent pain condition. Co-codamol was currently prescribed to nearly 24% of the sample, followed by tramadol and codeine. Therefore following the required washout period between the baseline visit and commencing codeine therapy 48 hours later at visit two it was anticipated that codeine response as defined earlier would be observed at a higher frequency in the EM phenotype participants.

A 30% score reduction on a NRS scale has been investigated and validated as a clinical significant marker of response in a persistent pain population[35]. By using the 30% reduction as a marker of codeine response the mean “average pain” in the last 24 hours was deemed to be the most suitable option to detect codeine response. A substantial amendment to the study inclusion criteria was required to allow potential participants to be recruited who had “daily

worse pain" ≥4 on a 0-10 NRS instead of "average pain". Study participants did comment during completion of questionnaires at visits that the nature of their persistent pain often makes it difficult to score an "average pain" score. A more substantial codeine response rate may have been observed in this study if "worst pain" in 24 hours was used as the codeine responder marker NRS instead of "average pain".

Although only 25% of the sample were defined as codeine responders using a ≥30% reduction in average pain NRS as a marker, overall pain severity and pain interference was significantly reduced at the $p<0.05$ level. However if a marker of ≥30% reduction in mean day0-day4 pain severity scores compared to baseline is applied to define codeine response only 13.6% of the sample would have been categorised as a codeine responder.

Overall improvement in health at the end of the study period was reported in 39.52% through the PGIC questionnaire, with 42.74% reporting no change and 17.74% reporting a worse health state. Although only 25% of the EM phenotypes achieved the defined codeine responder status, it is apparent that a large proportion were gaining some benefit from codeine therapy which is supported by the very significant reduction in pain interference scores indicating improvements in sleep, mood, anxiety, mobility, work, relationships with others and general activity. If a marker of ≥30% reduction in mean day0-day4 pain inference scores compared to baseline is applied to define codeine response then 36.8% of the sample would have been categorised as a codeine responder.

Concurrent prescribed medication was allowed to continue during the study period if confirmed they were not CYP2D6 inhibitors (Appendix 14.6). Participants were also asked if they were taking any "over the counter" medications, treatments or herbal supplements. These procedures were undertaken to assess the impact, if any, of multiple CYP2D6 substrates and the possibility of individual's CYP2D6 autophenocopying through substrate saturation and ultimate inhibition of the enzyme.

There have been multiple studies investigating the inhibitory effects of a particular drug of interest on CYP2D6 activity. However there is no substantial publications investigating the possibility of accumulative inhibitory effect of multiple concurrent CYP2D6 substrates which can saturate the enzyme. In a persistent pain population, polypharmacy for multiple co-existing conditions such as depression and cardiovascular disease are common. Therefore individuals may be taking several CYP2D6 substrates, which in theory could prevent full efficacy from analgesic prodrugs reliant on CYP2D6 enzyme for bio-transformation. Twelve individuals (9.6%)

were concurrently taking three or four CYP2D6 substrates prescribed four during the study period (not including the study medication). On comparison of urinary total morphine collected on day 4, six participants from this group had lower than expected concentrations and were categorised as codeine non-responders from their reported “average pain” scores. However in this study no significance on number of CYP2D6 substrates, urinary total morphine, urinary morphine:creatinine ratio and codeine response could be identified. Further research is warranted to investigate if CYP2D6 autophenocopying from multiple co-prescribed substrates impacts on analgesic efficacy of prodrug analgesics.

Five participants categorised as codeine non-responders were identified as taking CYP2D6 inhibitors during the course of the study (1xEM AS 1, 4xEM AS 2). Three EM (AS 2) participants were prescribed oral contraceptives which were permitted in the study design on ethical grounds. One EM (AS 2) was prescribed Diltiazem (anti-hypertensive) which has since been classified by the FDA as a weak CYP2D6 inhibitor (≥1.25 but < 2-fold increase in AUC or 20-50% decrease in clearance[26]). One EM (AS 1) reported taking Benadryl® for hay fever during the study period. Diphenhydramine, the active ingredient of Benadryl®, has been noted as a moderate CYP2D6 inhibitor[36-40]. In these five participants, CYP2D6 phenocopying has probably occurred with up to a 50% reduction in enzyme activity. This would result in the CYP2D6 genotype inferred EMs (AS 2) being inhibited to the activity level 1 and the EM (AS 1) to level 0.5, the IM phenotype.

Three EM participants, (AS 1, AS 1.5 and AS 2), down titrated and ceased taking the CYP2D6 strong inhibitors paroxetine or fluoxetine a minimum of 3 days before the baseline visit. The EM AS 1.5 and AS 2 were both categorised as codeine non-responders ceasing the strong inhibitors 3 and 9 days prior to baseline visit. The wash out period for these participants may have not been adequate to allow for systematic clearance of paroxetine or fluoxetine resulting in short term persistent CYP2D6 inhibition. Juřica and Žourková (2013)[41] determined the minimum wash out period to prevent persistent CYP2D6 inhibition was dependant on how long paroxetine therapy had been given.

Following short courses of paroxetine (6 weeks of treatment) the recommended minimum wash out period to prevent persistent inhibition is four weeks. Following courses of paroxetine longer than 18 weeks (on average), persistent CYP2D6 inhibition can still be present for longer than six weeks from stopping the drug. Juřica and Žourková[41] (2013)[41] recommended washout periods post paroxetine could reasonable be applied to fluoxetine due to they are both SRRIs and

strong CYP2D6 inhibitors. However the EM (AS 1) who ceased fluoxetine seven days prior to baseline visit was categorised as a codeine responder, but very low levels of urinary total morphine metabolites (equivalent level expected of a CYP2D6 PM) were detected in the day 4 urine sample. The low urinary morphine metabolite concentrations may have occurred through persistent CYP2D6 inhibition from the previous fluoxetine therapy or the participant's day 4 urine sample was collected a substantial time after the last codeine dose.

Participants were instructed to collect the Day 4 sample approximately one to two hours after the morning codeine dose. Therefore it is possible that this participant may have collected the urine sample before the morning codeine dose. Participants were not asked to record the time the last codeine dose taken and when the urine sample was collected, therefore the cause of the low urinary morphine metabolite concentrations cannot be determined. If the participant did collect the urine sample as instructed, one to two hours post codeine dose then persistent CYP2D6 inhibition from the previous fluoxetine is the likely cause of low urinary morphine concentration levels. However this participant reported a 36% analgesic response in mean day0-day4 "average pain"scores when compared to baseline. Categorised as a codeine responder it seems unlikely that persistent CYP2D6 inhibition is occurring unless the participant experienced a placebo analgesic response. A placebo analgesic response is classed as a reduction in pain resulting from the individual's expectation that a treatment given has analgesic efficacy[42]. Placebo analgesic response was also observed in two CYP2D6 PMs (reduction of 20% and 28% in mean day0-day4 average pains compared to baseline) and one IM (28% reduction when compared to baseline) who also had negligible urinary total morphine metabolites recorded in the day 4 urine sample.

11.2 FREQUENCY OF CYP2D6 PHENOTYPES

This study found the frequency of CYP2D6 phenotypes in a persistent pain population to be similar to those expected to be seen in a general Caucasian population for the PM phenotype only. The intermediate and ultra-rapid metaboliser phenotype frequency was considerably smaller than seen in a general population. For safety reasons, potential participants were excluded from taking part if they had previously tried and suffered intolerable side effects to morphine, codeine, co-codamol or tramadol. 595 approached individuals with persistent pain were classed as "failed screens" (received study information, declined study entry) due to previous intolerable side effects. This exclusion criteria may have excluded potentially

participants who were PM, IM and UM phenotypes. There have been few publications investigating the adverse drug reactions (ADRs) experience in PMs and IMs following oral codeine. Mikus *et al.,* (1997)[43] and Eckhardt *et al.,* (1998)[44] selected small sample sizes of healthy volunteers to investigate codeine related ADRs in PM and EM phenotypes. Mikus *et al.,* (1997)[43] found PMs did report gastrointestinal side effects, however at a reduced frequency when compared EMs following 60mg oral codeine. Whereas Eckhardt *et al.,* (1998)[44] identified that there was no significant difference between the frequency and severity of adverse side effects such as sedation, nausea and dry mouth following 170mg oral codeine dose in EM and PM individuals. This study found that there was no statistical significance in CYP2D6 phenotype/activity score, codeine responder status and reported ADRS of headache, dry mouth, nausea, drowsiness and constipation. The frequency of gastrointestinal ADRS such as constipation are reduced in PM and IM phenotypes when compared to EMs. These findings support the results from Mikus *et al.,* (1997)[43] and Eckhardt *et al.,* (1998)[44] suggesting that PM and IM phenotypes will suffer from unnecessary codeine related ADRs with no possible analgesic response.

This study found that UMs also report ADRS although not to the severity requiring withdrawal from study, Therefore it is reasonable to consider that PM, IM and UM phenotypes may have declined to participate due to previous lack of benefit from codeine and intolerable side effects. Further research is required to examine the true prevalence of CYP2D6 phenotypes in a persistent pain population. This may be achieved by pre-emptive CYP2D6 genotyping all new referrals to a specialist pain clinic which could aid clinical prescribing decisions.

Jannetto & Bratanow, (2009)[18] found from 61 persistent pain patients (predominantly Caucasian), 54% were EMs, 41% IMs and 5% PMs. Whereas this study found 84.5% were EMs, 4.65% IMs, 9.3% PMs and 1.55% UMs. This disparity is a clear example of the confusion that can occur when inferring CYP2D6 phenotype from genotype. Jannetto & Bratanow, (2009)[18] had selected adequate *CYP2D6* alleles for the genotyping array (*3,*4,*5,*6,*7,*8 and *2xN), however apart from the duplication *2xN all selected alleles were non-functional (AS 0). It appears Jannetto & Bratanow, (2009)[18] used the Dutch Pharmacogenetics Working Group (DPWG)[27] guidelines (1 functional + 1 non-functional allele) to categorise the IM phenotype and not the Clinical Pharmacogenetics Implementation Consortium (CPIC)[32] guidelines (1 non-functional allele + 1 reduced function allele). It is clear that there is still confusion over the level of CYP2D6 activity that constitutes the IM phenotype. If AS 1 had been used to infer the IM phenotype in this study the frequency of phenotypes would have been reported as EMs 61.04%,

IMs 29.46%, PMs 9.3% and UMs 1.55% suggesting that 40.31% of the study population would not obtain therapeutic analgesic efficacy from codeine and at risk of unnecessary potential ADRs due to CYP2D6 polymorphisms. Although this study enrolled twice as many participants than Jannetto & Bratanow, (2009)[18] the frequency of CYP2D6 phenotypes are not comparable.

This study found that CYP2D6 activity level is significant in therapeutic response to codeine and up to 28% of EMs (AS 1) is expected to respond to codeine compared to up to 42-43% of EMs (AS 1.5) and EMs (AS 2). It is reasonable from these findings to suggest that CYP2D6 AS 1 should not be allocated the EM phenotype. Codeine response is achievable in a minority of CYP2D6 AS 1, and therefore should not be allocated the IM phenotype which will indicate codeine non-response due to inadequate enzyme activity level. Therefore from the findings presented, a new phenotype classification of moderate metaboliser (MM) is proposed for CYP2D6 AS 1. The MM phenotype classification would represent the increased enzyme activity compared to IMs and reduced enzyme activity compared to EMs with the ability to partially respond to codeine.

11.3 CODEINE RESPONSE COULD BE PREDICTED USING MODEL 3 OR 4 BUT NOT CYP2D6 ACTIVITY SCORE

This study found that CYP2D6 phenotyping from oral fluid sampling, day 4 urinary total morphine metabolites and day 4 urinary morphine:creatinine ratio could not significantly be conducted. Oral fluid sampling was found to be ineffective at detecting codeine O-Demethylation metabolites at two hours post oral 30mg dose and therefore not a feasible method for phenotyping.

Analysis of urinary codeine O-Demethylation metabolites was conducted according to The Leeds Teaching Hospitals NHS Trust laboratory policy in an attempt to assess potential transferability to clinical practice. Therefore only total morphine, total codeine and creatinine concentrations were reported. According to laboratory practice total codeine metabolite concentrations were reported as greater than the higher quantification limit of 5000 (>5000) and not the precise concentration.

The mean urinary total morphine metabolites and mean morphine:creatinine ratio for each phenotype and AS score were used to develop four prediction models. Model one (urinary total morphine metabolite ranges) and model two (morphine:creatinine ratio ranges) were developed

to predict CYP2D6 activity level from a urine sample collected by the individual at home on the morning of day 4 of codeine 30mg QDS. No significance could be identified from either model. This may have occurred through poor compliance from the participant to collect the sample one to two hours after the morning codeine dose. A written reminder to the participant to collect the day 4 urine sample is printed on the day 3 pain questionnaires in the participant's study diary (Appendix 14.10). However the reminder did not stipulate the collection time should be one to two hours post morning codeine dose, this information was given orally at the visit 2 by the research nurse.

The patient's ability to recall medical information is often poor or inaccurate and is dependent on how the information has been communicate, the value of the information, the educational level, emotional status and age of the patient[45-48]. The collection of the urine sample may have been perceived by the participant as more important to remember than collection time post codeine dose. Therefore it is possible that some participants collected the day 4 urine samples not as instructed and the detected codeine O-Demethylation metabolites are not representative of the individuals CYP2D6 phenotype. Future research investigating CYP2D6 phenotyping from urinary codeine O-Demethylation metabolites should include documented last codeine dose and time of sample collection to eliminate doubt over the validity of the results.

Additionally, medication compliance (i.e. participants adhering to codeine 30mg QDS during study period) should also be considered. Lack of compliance would have a direct effect on the urinary codeine O-Demethylation metabolites concentrations on day 4 which could be lower than expected for the inferred phenotype. It has been documented that up to 50% of patients do not adhere to prescribed medication regimes[49-51]. However in this study, medication compliance ranged between 75-100%, with 82.4% of the participants fully compliant. This was achieved through participant's documenting doses taken in the participant diary and counting of returned medication and blister packaging at clinic visits. Therefore it is unlikely that low urinary codeine O-Demethylation metabolites observed in this study would be due to poor participant compliance in codeine therapy.

Two further models were developed using mean phenotypic ranges of urinary total morphine metabolite (model 3) and morphine:creatinine ratio ranges (model 4). These models were developed in an attempt to predict codeine response defined as ≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline score from a urine sample collected by the individual at home on the morning of day 4 of codeine 30mg QDS. The models

use a simple four tiered approach scored 0-3 with each tier containing a range value of either urinary total morphine or morphine:creatinine ratio. The likelihood of codeine response defined as a ≥30% reduction in mean day0-day4 “average pain” when compared to baseline is attributed to each model score with 0= probably will not respond to codeine, 1= may not respond to codeine, 2= expected to respond to codeine, 3=may not respond to codeine and potential for ADRs. Both models were at the p<.05 level at predicting codeine responder status according to the metabolite concentration levels present in the urine sample.

Both models had a 79% overall prediction success. Model 3 (urinary total morphine metabolites) was more slightly more sensitive but less specific that model 4 (urinary morphine:creatinine ratio). Both models could be used in clinical practice to assess codeine responder status following 4 days of codeine 30mgs QDS and may aid clinical prescribing decisions. However the models are only able to predict codeine responder status and not the individuals CYP2D6 phenotype or activity score. Further research is required to distinguish if model 3 and 4 are suitable for inferring a patient’s codeine responder status (i.e. codeine responder or codeine non-responder) following a single 30mg codeine dose.

12 TABLES, FIGURES AND GRAPHS

Table 4: Summary of reported pain states assessed by the S-LANSS questionnaire completed at the baseline visit for the enrolled (n=131) and ITT populations (n=125).

Pain state	Enrolled Population		Total (n=131) N (%)	ITT population/per protocol population		Total (n=125) N (%)
	Male (n=52) N (%)	**Female (n=79) N (%)**		**Male (n=51) N (%)**	**Female (n=74) N (%)**	
Neuropathic Pain	18/52 (34.62)	37/79 (46.83)	55/131 (41.98)	18/51 (35.30)	35/74 (47.30)	53/125 (42.74)
Nociceptive Pain	34/52 (65.38)	42/79 (53.16)	76/131 (58.02)	33/51 (64.70)	39/74 (52.71)	71/125 (57.26)
Total	52/52 (100)	79/79 (100)	131/131 (100)	51/51 (100)	74/74 (100)	124/125 (100)

Table 5: Current analgesics prescribed to the enrolled population (n=131) at study entry.

Drug	Analgesic efficacy dependent on CYP2D6 enzyme	CYP2D6 Inhibitor strength	Risk of DDIs & ADRs due to inhibited CYP2D6	Number of Prescribed Analgesics & Adjuvants Per Patient (n=131)							Total number of drugs (n=303) N (%)
				NONE N (%)	ONE N (%)	TWO N (%)	THREE N (%)	FOUR N (%)	FIVE N (%)	SIX N (%)	
				6 (4.6)	**36 (27.5)**	**33 (25.2)**	**30 (22.9)**	**21 (16.0)**	**2 (1.5)**	**3 (2.3)**	
Analgesic											
Strong Opioids											
Tramadol	Y	0	Y	0	3	6	12	5	2	2	**30 (9.9)**
Weak Opioids											
Co-codamol	Y	0	Y	0	12	11	4	6	0	1	**34 (11.2)**
Codeine	Y	0	Y	0	4	2	4	7	0	1	**18 (5.9)**
DF118	N	0	N	0	0	2	3	4	0	0	**9 (3.0)**
Co-dydramol	N	0	N	0	1	0	1	0	0	0	**2 (0.7)**
Non-opioid Analgesics											
Paracetamol	N	0	N	0	9	17	23	18	2	3	**72 (23.8)**
Aspirin	N	0	N	0	0	0	1	0	0	0	**1 (0.3)**
NSAID											
Diclofenac	N		N	0	2	4	10	6	1	1	**24 (7.9)**
Ibuprofen	N		N	0	3	5	3	7	0	1	**19 (6.8)**
Naproxen	N		N	0	0	5	4	4	0	0	**13 (4.3)**
Meloxicam	N		N	0	0	0	0	0	0	1	**1 (0.3)**
Etoricoxib	N		N	0	0	0	0	1	0	0	**1 (0.3)**
Ketoprofen	N		N	0	0	0	0	1	0	0	**1 (0.3)**
Movelat gel	N		N	0	0	0	0	0	1	0	**1 (0.3)**
Ibuprofen gel	N		N	0	0	0	1	1	0	1	**3 (1.0)**
Adjuvants											
TCA											
Amitriptyline	N	N/A	Y	0	2	8	11	10	2	2	**35 (11.6)**
Nortriptyline	N	N/A	Y	0	0	1	1	1	0	0	**3 (1.0)**
Anti-convuls-ants											
Pregabalin	N	N/A	N	0	0	3	4	5	1	2	**15 (4.9)**
Gabapentin	N	N/A	N	0	0	2	4	3	0	0	**9 (2.9)**
Lamotrigine	N	N/A	N	0	0	0	1	0	0	0	**1 (0.3)**
Other											
Duloxetine	N	50%	N	0	0	0	0	1	0	0	**1 (0.3)**
Baclofen	N	N/A	N	0	0	0	0	1	0	0	**1 (0.3)**
Lidocaine Patch	N	N/A	N	0	0	0	2	1	1	0	**3 (1.0)**
Capsaicin Cream	N	N/A	N	0	0	0	0	1	2	1	**4 (1.3)**
Diazepam	N	N/A	N	0	0	0	0	0	0	2	**2 (0.7)**

Table 6: CYP2D6 analgesic prodrugs prescribed to participants prior to study enrolment.

Drug	Males		Females		Total sample	
	Enrolled Population n n=52 (%)	***ITT Population n n=51 (%)***	**Enrolled Population n n=79 (%)**	***ITT Population n n=74 (%)***	**Enrolled Population n n=131 (%)**	***ITT Population n=125 (%)***
Co-codamol	11/52 (21.15)	*11/51 (21.56)*	20/79 (25.32)	*18/74 (24.32)*	31/131 (23.66)	*29/125 (23.2)*
Codeine	6/52 (11.54)	*6/51 (11.76)*	9/79 (11.39)	*9/74 (12.16)*	15/131 (11.45)	*15/125 (12.0)*
Tramadol	9/52 (17.31)	*9/51 (17.65)*	17/79 (21.52)	*15/74 (20.27)*	26/131 (19.85)	*24/125 (19.2)*
Codeine + Tramadol	1/52 (1.92)	*1/51 (1.96)*	1/79 (1.27)	*1/74 (1.35)*	2/131 (1.53)	*2/125 (1.6)*
Codeine + Co-codamol	0/52 (0)	*0/51 (0)*	1/79 (1.27)	*1/74 (1.35)*	1/131 (0.76)	*1/125 (0.8)*
Co-codamol + Tramadol	2/52 (3.85)	*2/51 (3.92)*	0/79 (0)	*0/74 (0)*	2/131 (1.53)	*2/125 (1.6)*
Total	29/52 (55.77)	*29/51 (56.86)*	48/79 (60.76)	*44/74 (59.46)*	77/131 (58.79)	*73/125 (58.4)*

Table 7a: Participants self-reported CYP2D6 analgesic prodrugs previously tried and failed to respond to for the management of their pain.

Drug	Males		Females		Total sample	
	Enrolled Population n=52 (%)	***ITT Population n=51 (%)***	**Enrolled Population n=79 (%)**	***ITT Population n=74 (%)***	**Enrolled Population n=131 (%)**	***ITT Population n=125 (%)***
Co-codamol	17/52 (32.69)	16/51 (31.37)	29/79 (36.71)	25/74 (33.78)	46/131 (35.11)	41/125 (32.8)
Codeine	14/52 (26.92)	14/51 (27.45)	14/79 (17.72)	14/74 (18.92)	28/131 (21.37)	28/125 (22.4)
Tramadol	19/52 (36.53)	19/51 (37.25)	31/79 (39.24)	29/74 (39.19)	50/131 (38.17)	48/125 (38.4)

Table 7b: Participants self-reported CYP2D6 analgesic prodrugs previously tried and failed to respond to for the management of their pain.

Drug	Males		Females		Total sample	
	Enrolled Population n n=52 (%)	**ITT Population n n=51 (%)**	**Enrolled Population n n=79 (%)**	**ITT Population n n=74 (%)**	**Enrolled Population n n=131 (%)**	**ITT Population n n=125 (%)**
Co-codamol	8/52 (15.38)	7/51 (13.72)	14/79 (17.72)	12/74 (16.21)	22/131 (16.79)	19/125 (15.2)
Codeine	6/52 (11.54)	6/51 (11.76)	8/79 (10.13)	8/74 (10.81)	14/131 (10.69)	14/125 (11.2)
Tramadol	9/52 (17.31)	9/51 (17.65)	18/79 (22.78)	17/74 (22.97)	27/131 (20.61)	26/125 (20.8)
Codeine + Tramadol	3/52 (5.77)	3/51 (5.88)	2/79 (2.53)	2/74 (2.7)	5/131 (3.82)	5/125 (4.0)
Codeine + Co-codamol	2/52 (3.85)	2/51 (3.92)	3/79 (3.8)	3/74 (4.05)	5/131 (3.82)	5/125 (4.0)
Co-codamol + Tramadol	4/52 (7.69)	4/51 (7.84)	10/79 (12.66)	9/74 (12.16)	14/131 (10.69)	13/125 (10.4)
All three drugs	3/52 (5.77)	3/51 (5.88)	1/79 (1.27)	1/74 (1.35)	4/131 (3.05)	4/125 (3.22)
Total	35/52 (67.31)	34/51 (66.67)	56/79 (70.89)	52/74 (70.27)	91/131 (69.47)	86/125 (68.8)

Table 8: CYP2D6 Phenotypes with activity score compared to prevalence in a general Caucasian population.

Phenotype	Activity Score	Males		Females		Sample		*Prevalence In Literature
		Enrolled n=52 (%)	**ITT n=51 (%)**	**Enrolled n=77 (%)**	**ITT n=74 (%)**	**Enrolled n=129 (%)**	**ITT n=125 (%)**	
Poor Metaboliser	0	4 /52 (7.69)	4 /51 (7.84)	8 /77 (10.39)	7 /74 (9.496	12/129 (9.3)	11/125 (8.8)	5-11%
Intermediate Metaboliser	0.5	5/52 (9.62)	5/51 (9.80)	1 /77 (1.30)	1 /74 (1.35)	6/129 (4.65)	6/125 (4.8)	10-15%
Extensive Metaboliser	1	12 /52 (23.08)	12 /51 (23.53)	20/77 (25.97)	20/74 (27.03)	32/129 (24.81)	32/125 (25.6)	70-80%
Extensive Metaboliser	1.5	9/52 (17.31)	9/51 (17.65)	9 /77 (11.69)	9 /74 (12.16)	18 /129 (13.95)	18 /125 (14.4)	
Extensive Metaboliser	2	21/52 (40.38)	20/51 (39.22)	38/77 (49.35)	36/74 (48.65)	59 /129 (45.74)	56 /125 (44.8)	
Ultra-rapid Metaboliser	>2	1 /52 (1.92)	1/51 (1.96)	1 /77 (1.30)	1 /74 (1.35)	2 /129 (1.55)	2 /125 (1.6)	5.5%

Table 9: CYP2D6 diplotypes and relevant phenotypes in the enrolled sample (n=129)

Diplo-type	Enrolled Population n=129						
	PM AS 0 n (%)	**IM AS 0.5 n (%)**	**EM AS 1 n (%)**	**EM AS 1.5 n (%)**	**EM AS 2 n (%)**	**UM AS >2 n (%)**	**TOTAL**
***1/*1**					19		19/129 (14.73)
***1/*2**					20		20 /129 (15.5)
***1/*4**			14				14/129 (10.85)
***1/*5**			5				5 /129 (3.88)
***1/*6**			1				1/129 (0.78)
***1/*9**				2			2/129 (1.55)
***1/*41**				7			7/129 (5.43)
***1XN/*1**						1	1/129 (0.78)
***1XN/*2**						1	1/129 (0.78)
***1XN/*4**					4		4/129 (3.1)
***2/*2**					10		10 /129 (7.75)
***2/*3**			2				2/129 (1.55)
***2/*4**			7				7/129 (5.43)
***2/*5**			1				1/129 (0.78)
***2/*9**				3			3/129 (2.33)
***2/*41**				6			6/129 (4.65)
***2XN/*4**					6		6/129 (4.65)
***3/*5**	1						1/129 (0.78)
***4/*4**	4						4/129 (3.1)
***4/*41**		3					3/129 (2.33)
***4XN/*4**	5						5/129 (3.88)
***4XN/*6**	1						1/129 (0.78)
***4XN/*9**		1					1/129 (0.78)
***4/*5**	1						1/129 (0.78)
***9/*41**			1				1/129 (0.78)
***9/*5**		1					1/129 (0.78)
***41/*5**		1					1/129 (0.78)
***41XN/*4**	1						1/129 (0.78)
TOTAL	13 (10.08)	6 (4.65)	31 (24.03)	18 (13.95)	59 (45.74)	2 (1.55)	129

Table 10: Comparison of genetically inferred CYP2D6 phenotype to current prescribed CYP2D6 reliant analgesic prodrugs in the enrolled population (n=129).

DRUGS	Total sample n=129					
	PM (AS 0)	**IM (AS 0.5)**	**MM (AS 1)**	**EM (AS 1.5)**	**EM (AS 2)**	**UM (AS >2)**
Co-codamol	3/129 (2.33)	1/129 (0.78)	8/129 (6.20)	8/129 (6.20)	11/129 (8.52)	0/129 (0)
Codeine	2/129 (1.55)	1/129 (0.78)	4/129 (3.10)	1/129 (0.78)	6/129 (4.65)	1/129 (0.78)
Tramadol	4/129 (3.10)	2/129 (1.55)	6/129 (4.65)	3/129 (2.33)	10/129 (7.75)	0/129 (0)
Codeine + Co-codamol	0/129(0)	0/129 (0)	0/129 (0)	0/129(0)	1/129 (0.78)	0/129 (0)
Codeine + Tramadol	0/129(0)	0/129 (0)	0/129 (0)	0/129 (0)	2/129 (1.55)	0/129 (0)
Co-codamol + Tramadol	1/129 (0.78)	0/129 (0)	0/129 (0)	0/129 (0)	1/129 (0.78)	0/129 (0)
T0TAL (%)	10/129 (7.75)	4/129 (3.10)	18 /129 (13.95)	12/129 (9.30)	31/129 (23.25)	1/129 (0.78)

Table 11: Comparison of genetically inferred CYP2D6 phenotype to previously tried and failed prescribed CYP2D6 reliant analgesic prodrugs in the enrolled population (n=129)

DRUGS	Total sample n=129					
	PM (AS 0)	**IM (AS 0.5)**	**EM (AS 1)**	**EM (AS 1.5)**	**EM (AS 2)**	**UM (AS >2)**
Co-codamol	2/129 (1.55)	0/129 (0)	4/129 (3.10)	4/129 (3.10)	10/129 (7.75)	0/129 (0)
Codeine	2/129 (1.55)	1/129 (0.78)	4/129 (3.10)	2/129 (1.55)	4/129 (3.10)	1/129 (0.78)
Tramadol	1/12 (0.78)	1/129 (0.78)	8/129 (6.20)	3/129 (2.33)	14/129 (10.85)	0/129 (0)
Codeine + Co-codamol	0/129 (0)	0/129 (0)	1/129 (0.78)	0/129 (0)	4/129 (3.10)	0/129 (0)
Codeine + Tramadol	0/129 (0)	0/129 (0)	1/129 (0.78)	3/129 (2.33)	1/129 (0.78)	0/129 (0)
Co-codamol + Tramadol	4/129 (3.10)	1/129 (0.78)	2/129 (1.55)	0/129 (0)	7/129 (5.43)	0/129 (0)
All 3 drugs	0/129 (0)	0/129 (0)	1/129 (0.78)	1/129 (0.78)	2/129 (1.55)	0/129 (0)
T0TAL (%)	9/129 (6.98)	3/129 (2.33)	21 /129 (16.27)	13/129 (10.07)	42/129 (32.55)	1/129 (0.78)

Table 12a: Average pain in last 24 hours calculated on a 0-10 numerical rating scale (NRS) from baseline, commencement of codeine treatment (day 0) until completion of study in the ITT population.

Average pain in last 24 hours NRS scale 0-10	Total Sample n=125				
	Mean	**SD (±)**	**Range**	**Median**	**IQR**
Baseline	6.31	±1.76	2-10	6	3
Day 0	6.00	± 1.94	1-10	6	2
Day 1	5.68	± 2.28	1-10	6	3
Day2	5.55	± 2.24	0-10	6	3
Day 3	5.51	± 2.37	0-10	6	3
Day 4	5.57	± 2.35	0-10	6	3
Mean day 0-4	5.66	± 2.11	1-10	5.8	2.8

Table 12B: Average pain in last 24 hours calculated on a 0-10 numerical rating scale (NRS) from baseline, commencement of codeine treatment (day 0) until completion of study in the ITT population for males and females.

Average pain in last 24 hours NRS scale 0-10	Males n=51					Females n=74				
	Mean	**SD (±)**	**Range**	**Median**	**IQR**	**Mean**	**SD (±)**	**Range**	**Median**	**IQR**
Baseline	6.06	±1.52	3-9	6	2	6.47	±1.9	2 - 10	7	3
Day 0	5.76	± 1.83	1-10	6	3	6.17	± 2.01	2 - 10	6	2
Day 1	5.45	± 2.01	1-10	6	3	5.84	± 2.45	1 - 10	6	4
Day2	5.45	± 2.08	0-10	6	3	5.62	±2.35	1 - 10	6	3
Day 3	5.31	± 2.21	0-10	6	3.5	5.65	± 2.49	0 -10	6	3
Day 4	5.31	± 2.28	0-10	6	4	5.74	± 2.39	0 -10	6	3
Mean day 0-4	5.46	± 1.95	1-10	5.6	2.7	5.81	± 2.21	1.2-10	6	2.8

Table 13a: ITT group Males (n=51) m-BPI-sf average pain in the last 24 hours calculated on a 0-10 numerical rating scale (NRS). Mean baseline score compared to mean day 0-day4 score in a two paired T Test.

T Test: Two Paired Samples

SUMMARY			Alpha	0.05		Hyp Mean Diff	0	
Groups	*Count*	*Mean*	*Std Dev*	*Std Err*	*t*	*df*	*Cohen d*	*Effect r*
Males BPI Average Pain Mean Baseline Score	51	6.058824	1.515411					
Males BPI Average Pain Day0-Day4 Mean Score	51	5.458824	1.947427					
Difference	51	0.6	1.499333	0.209949	2.857842	50	0.400178	0.374713

T TEST					
	p-value	*t-crit*	*lower*	*upper*	*sig*
One Tail	0.003101	1.675905			yes
Two Tail	0.006202	2.008559	0.178306	1.021694	yes

Table 13b: ITT group Females (n=74) m-BPI-sf average pain in the last 24 hours calculated on a 0-10 numerical rating scale (NRS). Mean baseline score compared to mean day 0-day4 score in a two paired T Test.

T Test: Two Paired Samples								
SUMMARY			Alpha	0.05		Hyp Mean Diff	0	
Groups	*Count*	*Mean*	*Std Dev*	*Std Err*	*t*	*df*	*Cohen d*	*Effect r*
Baseline BPI Average pain	74	6.486486	1.903445					
mean Average pain score	74	5.805405	2.209314					
Difference	74	0.681081	1.64022	0.190672	3.572009	73	0.415238	0.3857 2
T TEST								
	p-value	*t-crit*	*lower*	*upper*	*sig*			
One Tail	0.000316	1.665996			yes			
Two Tail	0.000632	1.992997	0.301073	1.061089	yes			

Table 14a: Pain severity scores calculated as a mean value for the total scores of worst, least, average and current pain within the last 24 hours for the ITT population.

Pain Severity in last 24 hours NRS scale 0-10	Total Sample n=125				
	Mean	**SD (±)**	**Range**	**Median**	**IQR**
Baseline	6.09	1.75	1.5-10	6	2.25
Day 0	5.93	1.99	1.25-10	6	3.25
Day 1	5.67	2.27	0.5-10	5.75	3.25
Day2	5.54	2.28	0.5-10	5.75	3.00
Day 3	5.57	2.40	0.25-10	5.75	3.5
Day 4	5.62	2.45	0-10	5.5	3.06
Mean day 0-4	5.67	2.17	0.85-10	5.7	2.95

Table 14.b: Pain severity scores calculated as a mean value for the total scores of worst, least, average and current pain within the last 24 hours for males and females of the ITT population.

Pain Severity in last 24 hours NRS scale 0-10	Males n=51					Females n=74				
	Mean	**SD (±)**	**Range**	**Median**	**IQR**	**Mean**	**SD (±)**	**Range**	**Median**	**IQR**
Baseline	5.73	1.61	2.25-9.25	5.5	2.5	6.25	1.82	1.5-10	6.25	2.4
Day 0	5.62	1.77	1.25-9.25	5.75	2.5	6.14	2.11	1.75-10	6.25	2.94
Day 1	5.37	1.98	1.25-9.25	5.25	2.25	5.88	2.44	0.5-10	5.75	3.19
Day2	5.42	2.03	1.25-9.25	5.5	3	5.63	2.45	0.5-10	5.75	3
Day 3	5.32	2.24	0.25-9.25	5.25	3.38	5.74	2.51	0.25-10	6	3.19
Day 4	5.34	2.30	0.25-9.25	5.25	3.88	5.81	2.54	0-10	5.63	2.75
Mean day 0-4	5.41	1.96	1.3-9.25	5.45	2.75	5.84	2.29	0.85-10	6.08	2.73

Table 15a: ITT group Males (n=51) m-BPI-sf pain severity (calculated from the NRS scores for "worst", "least", "average" and "current" pain within the last 24 hours) mean baseline score compared to mean day 0-day4 score in a two paired T Test.

T Test: Two Paired Samples

SUMMARY			Alpha	0.05		Hyp Mean Diff	0	
Groups	*Count*	*Mean*	*Std Dev*	*Std Err*	*t*	*df*	*Cohen d*	*Effect r*
Males BPI Pain Severity Mean Baseline Score	51	5.72549	1.614973					
Males BPI Pain Severity Mean Day 0-Day 4 Score	51	5.413294	1.959543					
Difference	51	0.312196	1.316	0.184277	1.694168	50	0.237231	0.232997

T TEST						
	p-value	*t-crit*	*lower*	*upper*	*sig*	
One Tail	0.048227	1.675905			yes	
Two Tail	0.096454	2.008559	-0.05793	0.682327	no	

Table 15b: ITT group Females (n=74) m-BPI-sf pain severity (calculated from the NRS scores for “worst”, “least”, “average” and “current” pain within the last 24 hours) mean baseline score compared to mean day 0-day4 score in a two paired T Test.

T Test: Two Paired Samples								
SUMMARY			Alpha	0.05		Hyp Mean Diff	0	
Groups	*Count*	*Mean*	*Std Dev*	*Std Err*	*t*	*df*	*Cohen d*	*Effect r*
Baseline BPI Pain Severity	73	6.25	1.836645					
mean pain score	73	5.834123	2.3081					
Difference	73	0.415877	1.42575	0.166871	2.492199	72	0.29169	0.281805
T TEST								
	p-value	*t-crit*	*lower*	*upper*	*sig*			
One Tail	0.007499	1.666294			yes			
Two Tail	0.014998	1.993464	0.083225	0.748529	yes			

Table 16a: Pain interference score calculated as a mean value for the total scores of pain interfered with general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life on a 0-10 NRS scale within the last 24 hours for the ITT population.

Pain Interference in last 24 hours NRS scale 0-10	Total Sample n=125				
	Mean	**SD (±)**	**Range**	**Median**	**IQR**
Baseline	6.14	2.11	0.1-10	6.29	2.86
Day 0	5.31	2.4	0.28-10	5	3.57
Day 1	5.09	2.58	0-10	4.86	3.72
Day2	4.9	2.59	0.1-10	4.71	4.00
Day 3	4.91	2.66	0-10	4.71	4.14
Day 4	4.91	2.73	0-10	5	4.43
Mean day 0-4	5.02	2.51	0.39-9.97	4.8	4.15

Table 16b: Pain interference score calculated as a mean value for the total scores of pain interfered with general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life on a 0-10 NRS scale within the last 24 hours for the males and females of the ITT population.

Pain Interference in last 24 hours NRS scale 0-10	Males n=51					Females n=74				
	Mean	**SD (±)**	**Range**	**Median**	**IQR**	**Mean**	**SD (±)**	**Range**	**Median**	**IQR**
Baseline	6.00	2.13	1-9.57	6.43	3.36	6.23	2.10	0.1-10	6.28	2.97
Day 0	5.25	2.28	0.86-9.57	5.43	3.58	5.35	2.49	0.28-10	4.93	3.57
Day 1	5.11	2.42	0.86-9.57	4.71	3.43	5.08	2.70	0-10	4.86	3.86
Day2	4.87	2.46	0.43-9.71	4.41	4.21	4.92	2.69	0.1-10	4.93	3.86
Day 3	4.88	2.64	0.29-9.86	4.43	4.26	4.92	2.69	0-10	4.71	4.11
Day 4	4.82	2.69	0-10	4.42	4.5	4.98	2.79	0-10	5.0	4.54
Mean day 0-4	4.99	2.68	0-10	4.42	4.05	5.05	2.59	0.39-9.97	4.9	3.95

Table 17a: ITT group Males (n=51) m-BPI-sf pain interference score (calculated from the NRS scores for pain interference with general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life within the last 24 hours) mean baseline score compared to mean day 0-day4 score in a two paired T Test.

T Test: Two Paired Samples

SUMMARY			Alpha	0.05		Hyp Mean Diff	0	
Groups	*Count*	*Mean*	*Std Dev*	*Std Err*	*t*	*df*	*Cohen d*	*Effect r*
Males BPI Pain Interference Baseline Mean Score	51	5.9684	2.143669					
Males BPI Pain Interference 0-Day 4 Mean Score	51	5.01848	2.429857					
Difference	51	0.94992	1.374501	0.192469	4.935454	50	0.691102	0.572349

T TEST

	p-value	*t-crit*	*lower*	*upper*	*sig*
One Tail	4.64E-06	1.675905			yes
Two Tail	9.29E-06	2.008559	0.563335	1.336505	yes

Table 17b: ITT group Females (n=74) m-BPI-sf pain interference score (calculated from the NRS scores for pain interference with general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life within the last 24 hours) mean baseline score compared to mean day 0-day4 score in a two paired T Test.

T Test: Two Paired Samples								
SUMMARY			Alpha	0.05		Hyp Mean Diff	0	
Groups	*Count*	*Mean*	*Std Dev*	*Std Err*	*t*	*df*	*Cohen d*	*Effect r*
Females BPI Pain Interference Mean Baseline Score	73	6.210685	2.106052					
Females BPI Interference Day 0-Day4 Mean Score	73	4.984137	2.540921					
Difference	73	1.226548	1.600852	0.187366	6.546282	72	0.766184	0.610832
T TEST								
	p-value	*t-crit*	*lower*	*upper*	*sig*			
One Tail	3.75E-09	1.666294			yes			
Two Tail	7.5E-09	1.993464	0.853041	1.600054	yes			

Table 18: Analgesic response defined as a ≥30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline for the ITT population.

Analgesic response	Males n=51		Females n=74		Total Sample n=125	
	Responder (≥ 30% in pain scores)	**Non-responder (< 30% reduction)**	**Responder (≥ 30% in pain scores)**	**Non-responder (< 30% reduction)**	**Responder (≥ 30% in pain scores)**	**Non-responder (< 30% reduction)**
Number (%)	10/51 (19.61)	41/51 (80.39)	16/74 (21.62)	58/74 (78.38)	26/125 (20.8)	99/125 (79.2)
Mean	49%	-1%	47%	0%	48%	-1%
SD (±)	0.19	0.22	0.16	0.17	0.17	0.19
Range	31-80 %	-113- 28%	30-85%	-50-29%	30-85%	-113-29%
Median	40%	3%	41%	0%	40%	0%
IQR	29%	14%	19%	19%	24%	16%

Table 19a: Analgesic response defined as a ≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline for the ITT population per phenotype.

Analgesic response	Total Sample n=125			
	Responder (≥ 30% in pain scores) in sample N (%)	**Response within phenotype (%)**	**Non-responder (< 30% reduction) in sample N (%)**	**Non response within phenotype (%)**
PM (AS 0)	0/125 (0)	0/11 (0)	11/125 (8.8)	11/11 (100)
IM (AS 0.5)	0/125 (0)	0/6 (0)	6/125 (4.8)	6/6 (100)
MM (AS 1)	5/125 (4.0)	5/32 (15.62)	27/125 (21.6)	27/32 (84.38)
EM (AS 1.5)	4 /125 (3.2)	4/18 (22.22)	14/125 (11.2)	14/18 (77.78)
EM (AS 2)	17/125 (13.6)	17/56 (30.36)	39 /125 (31.2)	39/56 (69.64)
UM (AS ≥2)	0/124 (0)	0/2 (0)	2/125 (1.6)	2/2(100)

Table 19b: Analgesic response defined as a ≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline for the ITT population per phenotype in males and females.

Analgesic response	Males n=51				Females n=74			
	Responder (≥ 30% in pain scores) in sample N (%)	**Response % within phenotype**	**Non-responder (< 30% reduction) in sample N (%)**	**Non response % within pheno-type**	**Responder (≥ 30% in pain scores) in sample N (%)**	**Response % within phenotype**	**Non-responder (< 30% reduction) in sample N (%)**	**Non response % within phenotype**
PM (AS 0)	0/51 (0)	0/4 (0)	4/51 (7.84)	4/4 (100)	0 (0)	0/7 (0)	7/74 (9.46)	7/7 (100)
IM (AS 0.5)	0/51 (0)	0/0 (0)	5/51 (9.8)	5/5 (100)	0 (0)	0/1 (0)	1/74 (1.35)	1/1 (100)
MM (AS 1)	1/51 (1.96)	1/12 (8.33)	11/51 (21.57)	11/12 (91.67)	4/74 (5.41)	4/20 (20.0)	16/74 (21.62)	15/20 (75.0)
EM (AS 1.5)	2/51 (3.92)	2/9 (22.22)	7 /51 (13.73)	7/9 (77.78)	2/74 (2.7)	2/9 (22.22)	7/74 (9.496	7/9 (77.78)
EM (AS 2)	7 /51 (13.73)	7/20 (35.0)	13/51 (25.5)	13/20 (65.0)	10/74 (13.51)	10/36 (27.78)	26/74 (35.14)	26/36 (72.22)
UM (AS 3)	0/51 (0)	0/1 (0)	1 /51 (1.96)	1/1 (100)	0/74 (0)	0/1 (0)	1/74 (1.35)	1/1 (100)

Table 20: Estimates of codeine response within CYP2D6 EM phenotype using exact binominal distribution with a 95% confidence interval

Phenotype	Mean responder rate	Standard deviation	Sample number	Confidence coefficient	Standard error (1.96XSD)/ √sample size)	Upper level (mean +SE)	Lower level (mean-SE)
PM	0	0	11	1.96	0	0	0
IM	0	0	6	1.96	0	0	0
EM AS 1	0.1563	0.368902	32	1.96	0.127818	0.284068	0.028432
EM AS 1.5	0.2222	0.427793	18	1.96	0.19763	0.419852	0.024592
EM AS 2	0.3036	0.463961	56	1.96	0.121519	0.42509	0.182053
UM AS 3	0	0	2	1.96	0	0	0

Fig 3: Bar graph of mean codeine responder rate within the CYP2D6 EM phenotype in relation to activity score. Whiskers reflect standard error value from table 20.

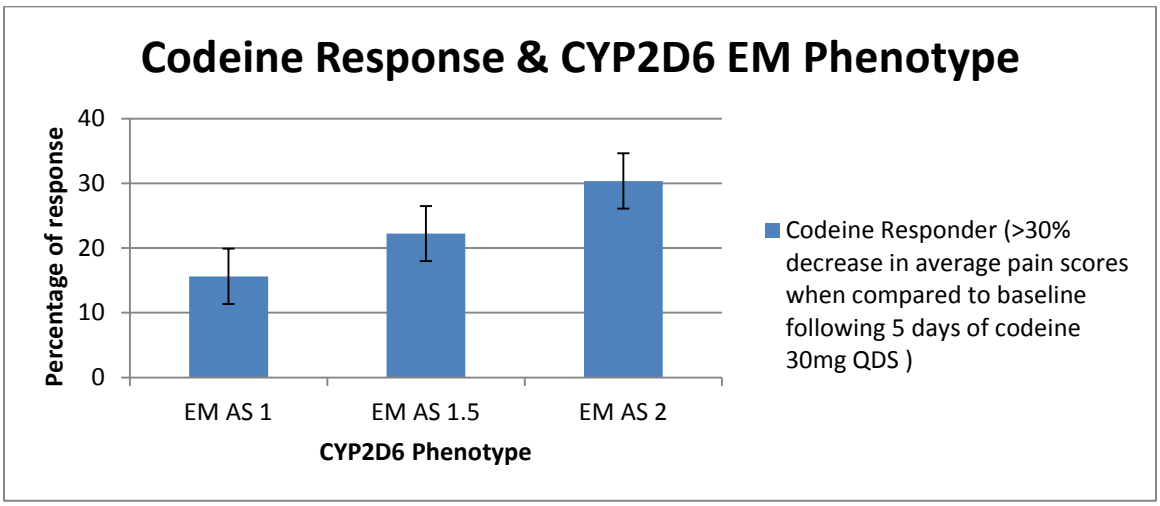


Table 21: Logistic regression analysis of CYP2D6 activity score and codeine response in the ITT group (n=125).

Logistic Regression Analysis of CYP2D6 Activity score and Codeine response

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	activity score	.963	.404	5.674	1	.017	2.621	1.186	5.790
	Constant	-2.841	.712	15.925	1	.000	.058		

a. Variable(s) entered on step 1: activity score.

Table 22: Urinary O-Demethylation total morphine (ng/L) metabolites detected in urine samples collected by the participants at home on the morning of Day 4 (following 30mg Codeine QDS). Results tabulated for each phenotype and activity score according to codeine responder status in the ITT population (n=124).

Urinary Total Morphine: Total Sample n=124						
Responder (≥ 30% reduction in mean day 0-day 4 average pain NRS scores)						
	PM (AS 0)	**IM (AS 0.5)**	**MM (AS 1)**	**EM (AS 1.5)**	**EM (AS 2)**	**UM (AS >2)**
Number (%)	0/124 (0)	0/124 (0)	5/124 (4.03)	4/124 (3.23)	17/124 (13.71)	0/124 (0)
Mean	0	0	1754.6	2523.75	3329.47	0
SD (±)	0	0	1661.56	1634.72	28822.71	0
Range (ng/L)	0	0	314-4380	75-3460	82-9850	0
Median	0	0	1528	3280	3090	0
IQR	0	0	1769	861.25	3130	0
Non-responder (< 30% reduction in mean day 0-day 4 average pain NRS scores)						
Number (%)	11/124 (8.87)	6/124 (4.84)	26/124 (20.97)	14/124	11/124 (8.87)	6/124 (4.84)
Mean	44.18	415.16	1444.65	2925.43	2846.08	5330
SD (±)	39.66	317.83	1342.90	2410.52	2226.72	3464.82
Range (ng/L)	0-111	104-1020	92-5800	489-7880	136-10200	2880-7780
Median	33	315	1075	1835	2140	5330
IQR	57	146.25	1280.25	3947.5	1756	2450

Fig 4a: Base-10 logarithm of median day 4 urinary total morphine metabolites for each CYP2D6 phenotype and activity score of participants defined as codeine non-responders (<30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline). Box =25th and 75th percentiles; bars=minimum and maximum values (n=124)

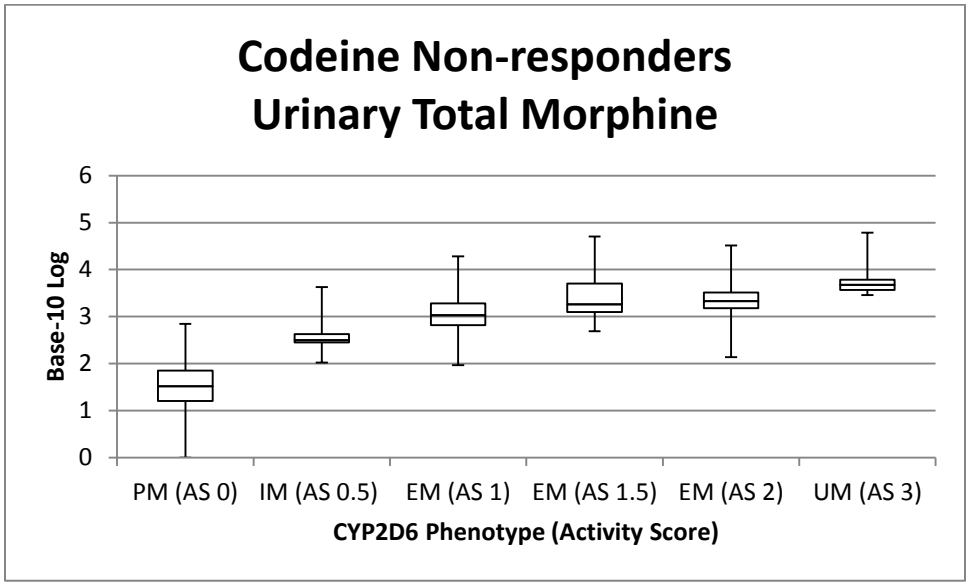


Fig 4b: Base-10 logarithm of median day 4 urinary total morphine metabolites for each CYP2D6 phenotype and activity score of participants defined as codeine responders (≥30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline). Box =25th and 75th percentiles; bars=minimum and maximum values (n=124)

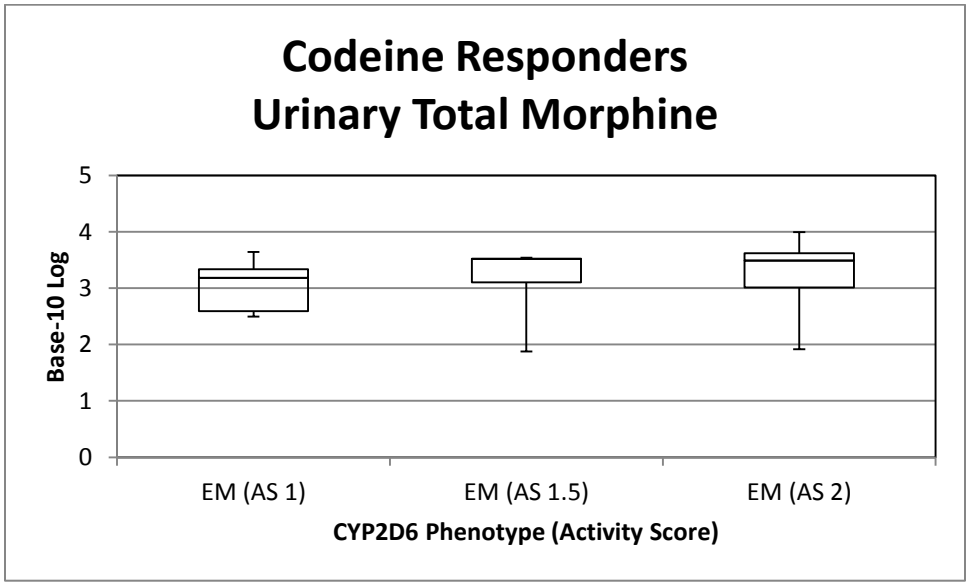


Fig 5a: Individual Value Plot chart of day 4 urinary total morphine metabolites for each CYP2D6 phenotype/activity score of participants defined as codeine non-responders (<30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline).

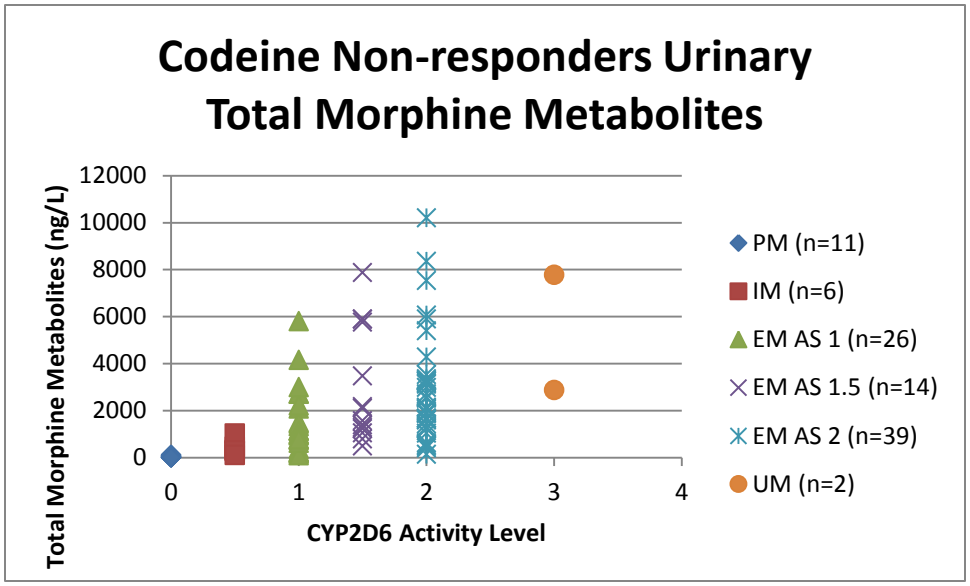


Fig 5b: Individual Value Plot chart of day 4 urinary total morphine metabolites for each CYP2D6 phenotype/activity score of participants defined as codeine responders (≥30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline).

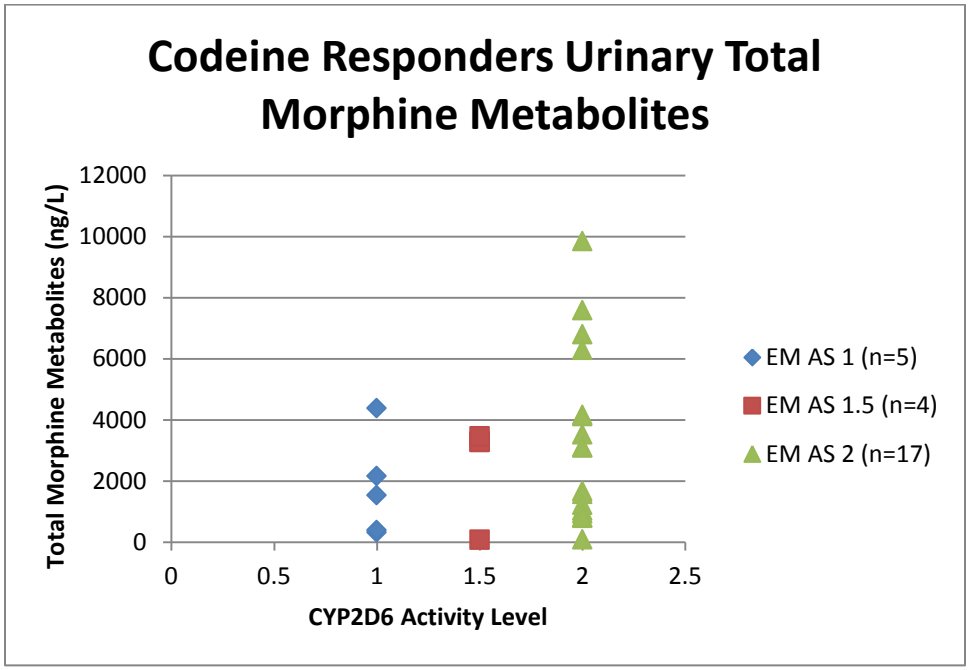


Table 23: morphine:creatinine ratio (urinary total morphine/creatinine concentration) detected in urine samples collected by the participants at home on the morning of Day 4 (following 30mg Codeine QDS). Results tabulated for each phenotype and activity score according to codeine responder status in the ITT population (n=124).

morphine:creatinine ratio (urinary total morphine/creatinine concentration): Total Sample n=124						
Responder (≥ 30% reduction in mean day 0-day 4 average pain NRS scores)						
	PM (AS 0)	**IM (AS 0.5)**	**MM (AS 1)**	**EM (AS 1.5)**	**EM (AS 2)**	**UM (AS >2)**
Number (%)	0/124 (0)	0/124 (0)	5/124 (4.03)	4/124 (3.23)	17/124 (13.71)	0/124 (0)
Mean	0	0	271.8	347	480.82	0
SD (±)	0	0	228.06	243.93	389.56	0
Range	0	0	33-498	17-584	14-1791	0
Median	0	0	299	393.5	450	0
IQR	0	0	445	243	269	0
Non-responder (< 30% reduction in mean day 0-day 4 average pain NRS scores)						
Number (%)	11/124 (8.87)	6/124 (4.84)	26/124 (20.97)	14/124 (11.29)	39/124 (31.45)	2/124 (1.61)
Mean	6.91	35.83	197.96	307	389.69	646.5
SD (±)	4.46	7.14	150.23	177.35	263.18	12.02
Range	0-15	26-45	17-711	58-654	22-1222	638-655
Median	7	37.5	178.5	274.5	324	646.5
IQR	4.5	9	130.75	294.5	349.50	8.5

Fig 6a: Individual Value Plot od Day 4 urinary morphine:creatinine ratio for each CYP2D6 phenotype/activity score of participants defined as codeine non-responders (<30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline).

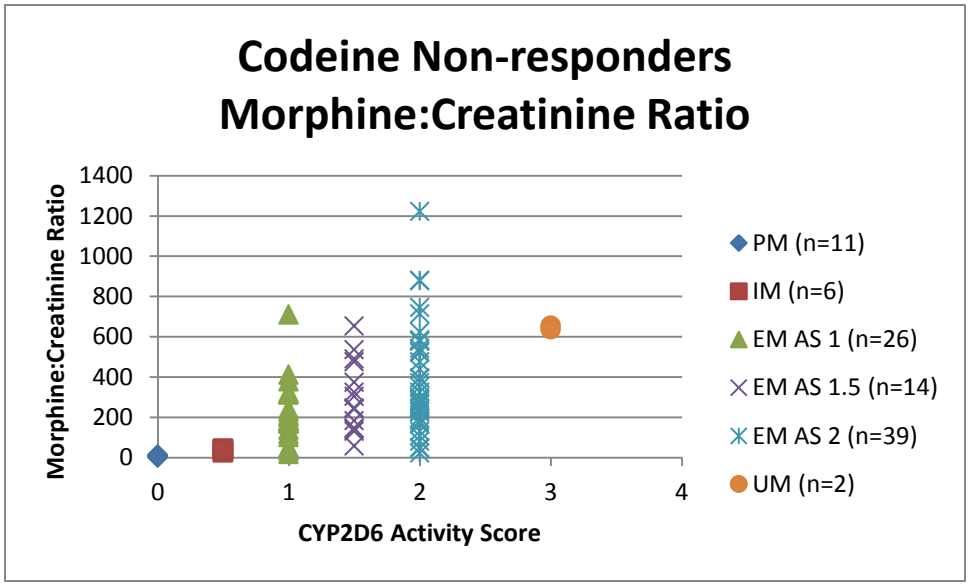


Fig 6b: Individual Value Plot od Day 4 urinary morphine:creatinine ratio for each CYP2D6 phenotype/activity score of participants defined as codeine responders (≥30% reduction in mean day0-day4 “average pain” 0-10 NRS score when compared to baseline).

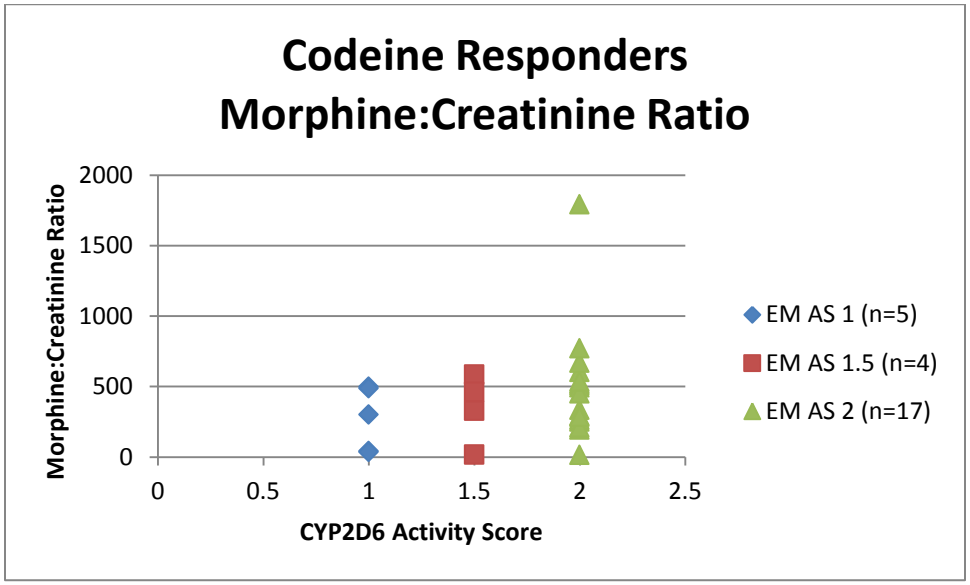


Table 24: A one way between CYP2D6 phenotypes ANOVA was conducted in the ITT group (n=124) to compare the effect of CYP2D6 activity score on the log transformed urinary total morphine metabolites

ANOVA								
Sources	*SS*	*df*	*MS*	*F*	*P value*	*F crit*	*RMSSE*	*Omega Sq*
Between Groups	30.53324	5	6.106648	32.9611	7.34E-21	2.291828	1.777329	0.565072
Within Groups	21.67639	117	0.185268					
Total	52.20963	122	0.427948					

Table 25: A one way between CYP2D6 phenotypes ANOVA was conducted in the ITT group (n=124) to compare the effect of CYP2D6 activity score on the log transformed morphine:creatinine ratio

ANOVA								
Sources	*SS*	*df*	*MS*	*F*	*P value*	*F crit*	*RMSSE*	*Omega Sq*
Between Groups	28.40353	5	5.680707	38.42573	3.58E-23	2.291828	1.919225	0.60339
Within Groups	17.29681	117	0.147836					
Total	45.70035	122	0.374593					

Table 25: Model 1: A novel model and scoring system for predicting CYP2D6 activity score from urinary total morphine metabolites (ng/L) calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

CYP2D6 AS	**CYP2D6 Pheno-type**	**Mean Total Morphine Ranges (ng/L)**		**Suggested model for predicting CYP2D6 AS**	**Scoring code**	**Rational**
		Codeine non-responder	Codeine responder	Total Morphine Ranges (ng/L)		
0	PM	44.2	0	0-150	0	<300ng/L is classed as a negative cut off point in codeine drug screens
0.5	IM	415.2	0	151-500	0.5	Severely reduced function and comparable to PMs
1	EM	1444.7	1754.6	501-2000	1	Expected to respond to codeine
1.5	EM	2925.4	2523	2001-3000	1.5	
2	EM	2846.1	3329.5	3001-7500	2	
3	UM	5330	0	>7501	3	Potential for ADRS

Table 26: Model 2: A novel model and scoring system for predicting CYP2D6 activity score from morphine:creatinine ratio (total morphine/total creatinine) calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

CYP2D6 AS	**CYP2D6 Pheno-type**	**Mean Total Morphine:creatinine ratio** (ng/L)		**Suggested model for predicting CYP2D6 AS**	**Scoring code**	**Rational**
		Codeine non-responder	Codeine responder	morphine:creatinine ratio ranges		
0	PM	6.91	0	≤20	0	<300ng/L is classed as a negative cut off point in codeine drug screens
0.5	IM	35.83	0	21-100	0.5	Severely reduced function and comparable to PMs
1	EM	197.96	271.8	100-300	1	Expected to respond to codeine
1.5	EM	307	347	301-375	1.5	
2	EM	389.69	480.82	375-600	2	
3	UM	646.5	0	>601	3	Potential for ADRS

Table 27: Model 3: A novel model and scoring system for predicting codeine response (≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline) from urinary total morphine metabolites (ng/L) calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

CYP2D6 AS	CYP2D6 Pheno-type	Mean Total Morphine Ranges (ng/L)		Suggested model for predicting codeine response		Scoring code	Rational
		non-responder	responder	Total Morphine Ranges (ng/L)	Expected codeine response		
0	PM	44.2	0	0-499	Probably will not respond to codeine	0	Includes PM and IM phenotypes
0.5	IM	415.2	0				
1	EM	1444.7	1754.6	500-1499	May not respond to codeine	1	Includes EM AS 1 phenotype or individuals phenocopying
1.5	EM	2925.4	2523	1500-7500	Should respond to codeine	2	Includes EMs AS 1.5 and AS 2: Expected to respond to codeine
2	EM	2846.1	3329.5				
3	UM	5330	0	>7500	May not respond and potential ADRS	3	Potential for ADRS

Table 29: Logistic regression of Model 3 scoring system for predicting codeine response (≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline) from urinary total morphine metabolites (ng/L) calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

		B	S.E.	Wald	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Step 1[a]	Predicted Codeine response status using Model 3 (Day 4 Total Morphine Metabolites)	2.63906	0.44320263	35.45627	2.608E-09	0.0714286	0.029965	0.170266
	Constant	1.540445	0.318104505	23.45054	1.282E-06	4.6666667		

Fig 7: ROC curve of Model 3 scoring system for predicting codeine response (≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline) from urinary total morphine metabolites (ng/L) calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

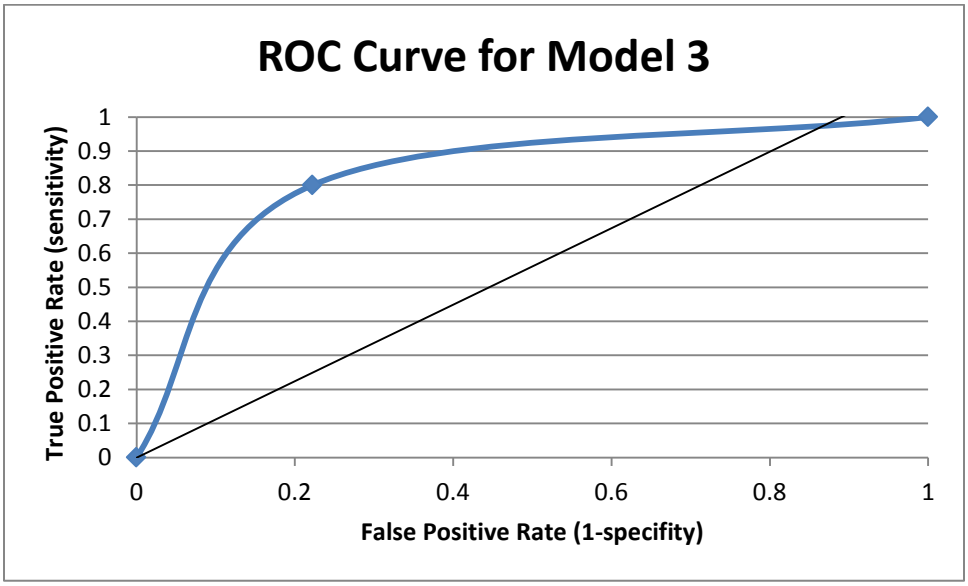


Table 28: Model 4: A novel model and scoring system for predicting codeine response (≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline) from morphine:creatinine ratio (total morphine/total creatinine) metabolites calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS

CYP2D6 AS	**CYP2D6 Pheno-type**	**Mean Total Morphine:creatinine (M:C) Ratio Ranges (ng/L)**		**Suggested model for predicting codeine response**		**Scoring code**	**Rational**
		non-responder	responder	M:C Ratio Ranges (ng/L)	Expected codeine response		
0	PM	6.91	0	0-100	probably will not respond to codeine	0	Includes PM and IM phenotypes
0.5	IM	35.83	0				
1	EM	197.96	271.8	100-250	may not respond to codeine	1	Includes MM phenotype or individuals phenocopying
1.5	EM	307	347	250-1000	should respond to codeine	2	Includes EMs AS 1.5 and AS 2: Expected to respond to codeine
2	EM	389.69	480.82				
3	UM	646.5	0	>1000	may not respond and potential ADRS	3	Includes UMs : Potential for ADRS

Table 30: Logistic regression of Model 4 and scoring system for predicting codeine response (≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline) from morphine:creatinine ratio (total morphine/total creatinine) metabolites calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

		B	S.E.	Wald	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Step 1[a]	Predicted Codeine response status using Model 4 (Day 4 Total Morphine:creatinine Ratio Metabolites)	2.77129	0.472383	34.41708	4.45E-09	0.062581	0.024794	0.157957
	Constant	1.998096	0.376761	28.12547	1.14E-07	7.375		

Fig 8: ROC curve of Model 4 and scoring system for predicting codeine response (≥30% reduction in mean day0-day4 "average pain" 0-10 NRS score when compared to baseline) from morphine:creatinine ratio (total morphine/total creatinine) metabolites calculated from urinary metabolites measured from a day 4 urine sample following oral codeine 30mg QDS.

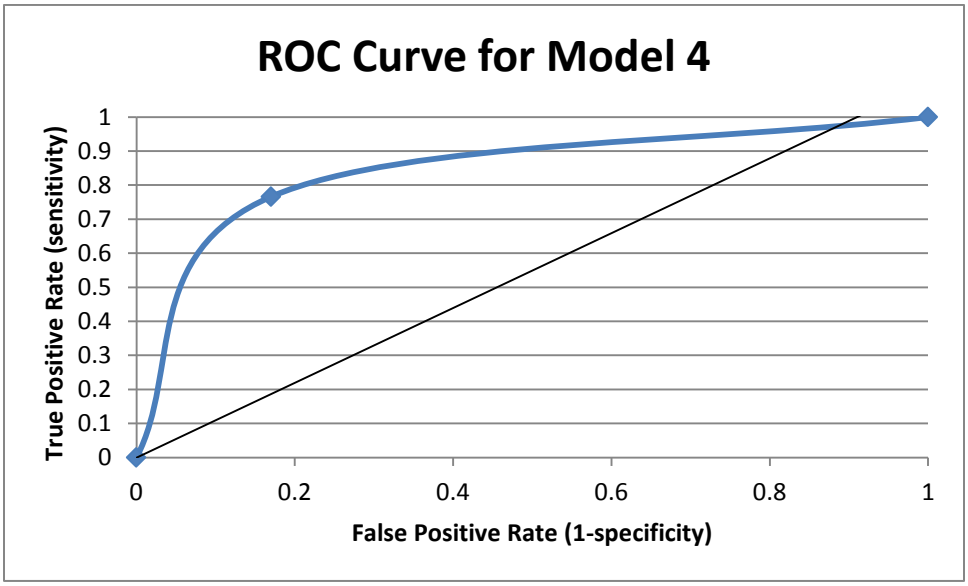


Table 31: Number of concurrent CYP2D6 substrates prescribed to participants during the study period in the ITT group (n=125).

CYP2D6 Pheno-type	Number of CYP2D6 substrates: Total Sample n=125									
	None N (%)		One N (%)		Two N (%)		Three N (%)		Four N (%)	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
PM (AS 0)	0	4 (3.2)	0	6 (4.8)	0	1 (0.8)	0	0	0	0
IM (AS 0.5)	0	1 (0.8)	0	4 (3.2)	0	0	0	0	0	1 (0.8)
EM (AS 1)	0	10 (8.0)	4 (3.2)	7 (5.6)	1 (0.8)	7 (5.6)	0	3 (2.4)	0	0
EM (AS1.5)	1 (0.80)	7 (5.6)	2 (1.6)	5 (4.0)	0	0	1 (0.8)	2 (1.6)	0	0
EM (AS 2)	5 (4.0)	11 (8.8)	8 (6.4)	11 (8.8)	2 (1.6)	12 (9.6)	1 (0.8)	3 (2.4)	1 (0.8)	2 (1.6)
UM (AS >2)	0	2 (1.6)	0	0	0	0	0	0	0	0
Total	6 (4.8)	35 (28.0)	14 (11.2)	33 (26.4)	3 (2.4)	20 (16.0)	2 (1.6)	8 (6.4)	1 (0.80)	3 (2.4)

Table 32: Clinician's Global Impression of Change (CPIC) matched to Participants Global Impression of Change (PGIC) for accuracy at the end of the study period

CGIC matched PGIC	Total sample n=125			
	Responders		Non-responders	
	YES	NO	YES	NO
PM (AS 0)	0	0	9/125 (7.2)	2/125 (1.6)
IM (AS 0.5)	0	0	2/125 (1.6)	4/125 (3.2)
EM (AS 1)	3/125 (2.4)	2/125 (1.6)	19/125 (15.2)	7/125 (5.6)
EM (AS 1.5)	4/125 (3.2)	0	11/125 (8.0)	3/125 (2.4)
EM (AS 2)	13/125 (10.4)	4/125 (3.2)	28/125 (22.4)	12/125 (9.6)
UM AS > 2)	0	0	1/125 (0.8)	1/125 (0.8)
Total	20/125 (16.0)	6/125 (4.8)	70/125 (56.0)	29/125 (23.2)

13 PUBLICATION PLAN

Finding from the study will be written up as part of a PhD thesis and published in relevant academic and healthcare professional journals over the next 12 months.

13.1 Poster Abstracts:

Interim results from the study have been presented at the following professional and academic conferences:

- April 2013: British Pain Society Annual Scientific Meeting, Bournemouth UK (Appendix .

Title: A POPULATION STUDY INTO THE PREVALENCE AND GENETIC PROFILE OF PATIENTS WITH CHRONIC PAIN WHO DO NOT RESPOND TO ORAL CODEINE: Oral Transudate Subset Results. (Awarded the 2013 Poster Prize)

- October 2013: European Federation of ISAP Chapters (EFIC) Annual Scientific Meeting, Florence Italy.

Title: CYP2D6 GENOTYPING IN A CHRONIC PAIN POPULATION: IS A FIFTH PHENOTYPE CLASSIFICATION OF 'MODERATE METABOLISER' REQUIRED FOR CONCORDANCE?

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15 APPENDICES

15.1 STUDY PROTOCOL

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.

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Funder	Dr Paul Schofield Medical Director & Consultant in Pharmaceutical Medicine Medical Directorate NAPP Pharmaceuticals Limited Cambridge Science Park Milton Road Cambridge CB4 0GW
Research Team Members	Co-investigator: Ms H E Radford Research Nurse: Mrs Suzanne Rogerson Leeds Pain Management Service D Ward, Old Day Unit, Seacroft Hospital Leeds LS14 6UH 0113 2063132/0113 2063131
Sponsor	The Leeds Teaching Hospitals NHS Trust
Trust(s) where research will take place	The Leeds Teaching Hospitals HNS Trust

EudraCT No: 2007-006184-70

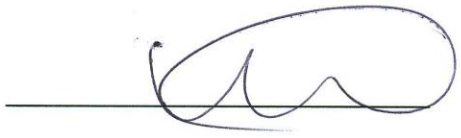
Protocol Number: A2007N

Signatures Page

A Population Study into the Prevalence and Genetic Profile of Patients with Chronic Pain who do not Respond to Oral Codeine

Final Version 3 (14/08/12)

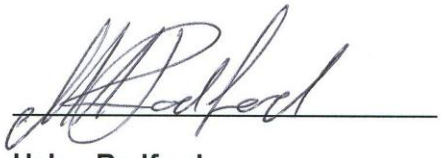
Written and approved by the following:



20/9/12

Karen Simpson
Chief Investigator

Date



20/SEP/2012

Helen Radford
Senior Research Nurse
/ Project Manager

Date

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Study Summary

Title	A population study into the prevalence and genetic profile of patients with chronic pain who do not respond to oral codeine
Short Title	Codeine non- responder study
Protocol Version Number and Date	Final Version 3 (14/08/12)
Methodology	Open Label
Study Duration	18 months
Study Centres	Single Centre
Objectives	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
Number of Subjects/Patients	150 subjects
Main Inclusion Criteria	Male or female Caucasian subjects, ages between 18-80 years. Patients with a chronic pain condition >3 months duration that has been diagnosed by a pain management specialist with moderate to severe chronic pain (.defined as a minimum score of 4 at screening and a minimum average daily pain score of 4 on the Modified Brief Pain Inventory-Short Form (m-BPI-sf), during pre-treatment)
Statistical Methodology and Analysis	The proportion of codeine non-responders will be estimated. Logistic regression will be used with genetic group and levels of codeine metabolites as predictors of the non-responders.

Summary of Amendments

Amendment Number	Date	Contents
Substantial amendment one	12th Feb 2010	• Addition of Poster Advert, no change to protocol
Substantial amendment two	8th December 2011	• Removal of Oral Transudate testing • Cover pg: addition of research nurse team member • Pg 2: updated signature page
Substantial amendment Three	14th August 2012	• Change to inclusion criteria number V from (page 5 and page 14): Patients with moderate to severe chronic pain (defined as a minimum of 40 mm pain score on the 100mm pain visual analogue scale (VAS) at screening and a minimum average daily pain score of 4 on Daily Pain Rating Scale (DPRS) during pre-treatment. To: Patients with moderate to severe chronic pain (defined as a score of 4 (out of 10) or above on worst pain in the last 24 hours (question 3) on the Brief Pain Inventory at screening and daily in the Patient Diary during pre-treatment.) • Removal of Patient information sheet and consent form from appendixes.

1. Introduction

This document is a research protocol and 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.

This is a single site population study. A sample of 150 patients will be enrolled from the Leeds Chronic Pain Clinic after obtaining their informed consent. Participants will attend the pain research clinic at Seacroft Hospital Leeds on three separate occasions. Their participation in this study will be no longer than 15 days.

Trial participants will receive the patient information sheet and consent form approximately 7 days before the planned screening visit. Each trial participant will be given ample time to make an informed decision as to whether to participate in the study and to ask questions before signing the informed consent form. At the screening visit, informed consent will be taken prior to any trial investigations. At this visit after signing the consent form, participants will be assessed on their suitability for this study using the inclusion/exclusion criteria. Blood samples will be taken for serum urea, creatinine, full blood count, electrolytes and liver enzymes.

Participants will then be asked to complete the following baseline questionnaires (appendix 18.5 to 18.8): - Modified Brief Pain Inventory-Short Form (m-BPI-sf), Leeds Assessment of Neuropathic Pain Scale (S-LANSS), and the SF8 quality of life questionnaire. A urine sample will also be obtained for dipstick analysis and pregnancy test for female participants who are of childbearing potential.

Patients will then be instructed to stop all prohibited medication (appendix 4).They will be issued with paracetamol as rescue medication for breakthrough pain during the washout phase and issued with a pain diary to complete over the next 48 hours. Participants will be instructed on how to complete the pain diary. The pain diary will be completed once a day before retiring to bed. They will be asked to complete the Modified Brief Pain Inventory-Short Form (m-BPI-sf) and any adverse events such as nausea or dizziness and any breakthrough analgesia used.

Participants will return to the pain research clinic following the 48 hour washout period. They will be asked to complete the following questionnaires: Modified Brief Pain Inventory-Short Form (m-BPI-sf) and SF8 quality of life questionnaire. A saliva sample will be collected for CYP2D6 genotyping. A urine sample will also be obtained for analysis of morphine /codeine metabolites.

At this visit participants will be given regular therapeutic oral doses of 30 mg codeine to take up to 4 hourly (maximum 120mg in 24 hours) over 5 days prior to returning for assessment. The first oral dose of codeine will be administered at this visit. and will return for their next visit approximately 5 days later.

During this period they will complete a pain dairy daily before retiring to bed. They will complete the Modified Brief Pain Inventory-Short Form (m-BPI-sf) and any adverse events such as nausea or dizziness plus any breakthrough analgesia used.

On the morning of day 4 the participant will collect an early morning sample of urine in a universal container supplied at visit 2. The participant will bring this sample with them to the clinic on day 5 where it will be processed for morphine/codeine metabolites.

After 5 days the participant will return to clinic for visit 3. A further set of questionnaires will be completed: - Modified Brief Pain Inventory-Short Form (m-BPI-sf) and SF8. Additionally global impression of change scales will be completed by the assessor (Clinical Global Impression of Change Scale – CGIC) and patient (Patient Global Impression of Change Scale – PGIC) and the pain diary examined for completeness. A further urine sample for morphine/codeine metabolites will also be collected at this visit.

Any adverse events such as nausea or dizziness will also be recorded. This will be the end of the study for the participant, who will recommence their regular analgesia or will be prescribed codeine if their pain has been effectively controlled. If neither is suitable the patient will be reviewed by a Pain Consultant in the chronic pain clinic for an assessment.

The participants will then be followed up by telephone 7 days following completing the study to check that there has been no late adverse events.

1.1 Background

Pharmacogenetics is the study of the dissimilarity in inter-individual response to drugs as the consequence of genetic differences. Clinical disparity in drug response may be as a result of pharmacokinetics or pharmacodynamics or it may be idiosyncratic. These differences may have a genetic basis. An example of this might be the situation where an individual has a suboptimal or even a complete lack of therapeutic response to a drug. The ability to predict clinical efficacy and identify these variations through an easily executed, repeatable, cost effective clinical test would be a valuable tool. The benefits may include enhanced patient compliance due to better clinical response, improved patient safety, and reduced costs: ultimately it may be seen as a step towards tailoring medical management to the individual. [2]

Chronic pain was originally defined as pain that has lasted 6 months or longer. More recently it has been defined as pain that persists longer than the temporal course of natural healing that is associated with a particular type of injury or disease process. [4] The International Association for the Study of Pain defines pain as an unpleasant sensory and affective experience induced by the exposure to noxious stimuli i.e. injury incipient or substantive in nature. [5]

Chronic pain may be related to a number of different medical conditions including diabetes, arthritis, migraine, previous trauma or injury and may worsen in response to environmental and/or psychological factors. There are a variety of treatment options for people with chronic pain. The goal of pain management is to provide symptom relief and improve an individual's level of functioning in daily activities.

A number of types of analgesics are used in the management of chronic pain, including COX-2 inhibitors, antidepressants, and opioids. Prescription of analgesics in the pain clinic follows the World Health Organisation Pain Relief ladder (6.) This is a three step approach to pain management. Step one is a non-opioid medication, step two is an opioid for mild to moderate pain and step three is an opioid for moderate to severe pain. Patients presenting with chronic pain are commenced on step one of the analgesic ladder which is usually paracetamol 1g every 4 hours. If the patient is still reporting significant pain after 2 weeks, it is common to proceed to a step two analgesic, particularly Codeine phosphate (up to 60mg every 4 hours) (7).

Investigational Agent

Codeine phosphate is an opium alkaloid, about 1/10 as potent as morphine, which acts via the central nervous system. Codeine is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about one hour. One component of pharmacokinetics is drug metabolism: the cytochrome P_{450} enzyme system plays a central role in this. Polymorphisms in the genes coding for this enzyme system have been identified and are a significant determinant of pharmacogenetic variability. One constituent of cytochrome P_{450} is the 2D6 isozyme which is responsible for the metabolism of a multitude of drugs including codeine phosphate. Metabolism of codeine by the cytochrome P_{450} 2D6 isozyme (CYP2D6) consists of O-demethylation to morphine. Morphine is subsequently metabolised to morphine-3- and morphine-6-glucuronide. There is evidence to support that the analgesic effects of codeine are primarily mediated through its morphine metabolites. Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. The plasma half life has been reported to be between 3 and 4 hours. [8]

a. Clinical Data to Date

It is estimated that 5 -10% of Caucasians metabolise codeine and other CYP2D6 substrates poorly as a result of non-functioning alleles of the CYP2D6 gene; 10-15% are termed intermediate metabolisers and possess weakened enzyme activity. Potentially, therefore, up to 25% of a Caucasian population will lack an optimal analgesic response to codeine. It is therefore important to study just Caucasians in this pilot study to reduce the group heterogeneity and also because there is evidence to suggest that there are differences between ethnic groups in metabolic efficiency. [9 & 10]

b. Rationale and Risk/Benefits

Genotyping techniques allow identification of those patients who are poor metabolisers. Urine testing for the excretion of morphine and its metabolites also permits measurement of CYP2D6 activity in vivo and identification of the poor metaboliser phenotype.

Patients with pain may have nociceptive, neuropathic or mixed pain states; this can be predicted using the S-LANSS score. Neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system where as Nociceptive pain is pain that occurs due to tissue damage or inflammation. In some cases the patient can present with a both types of pain which is classified as a mixed pain state.

The usual split in pain clinics is about 1/3 of each type of pain. It is postulated that those with neuropathic pain – that is difficult to manage but does respond in part to opioids – may be more likely to be sent to a specialist pain clinic if they are codeine non-responders. They may have had simple treatment in primary care that has failed due to pharmacogenetic reasons. This study will identify pain types as well as codeine non-response and will thus test this hypothesis.

2. Study Aims and Objectives

The primary objectives of the study are to:

- 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

The secondary objectives of the study are to:

- Investigate whether codeine non-responsiveness is different in nociceptive, neuropathic and mixed pain states

- Correlate genetic testing from saliva samples for CYP2D6 plus urine testing of morphine metabolites as predictors of codeine non-responsiveness

- Investigate the pharmacogenetics of codeine phosphate and its implications in clinical practice for chronic pain clinic attendees

3. Study Design

a. General Design

This is a single center population based study. The duration of the study for each patient will be no more than 15 days from screening to follow up. Patients will be recruited over a period of 18 months.

A diagram of the trial design, procedures and stages:

Procedures	Screening Visit (+/-1day)	Visit2 (+/-1day)	At home	Visit 3 (+/-1day)	Follow up (+/-1day)
	Day -2	Day 0	Day 4	Day 5	Via Telephone day 12
Informed Consent	x				
Vital signs	x	x		x	
Pain Questionnaires: m-BPI-sf and SF-8	x	x		x	
SLANSS	x				
Lab Safety Tests	x				
Global impression of change				x	
Recording AE's		x	x	x	x
Saliva sample for genetic testing		x			
Urine sample for opioid metabolites		x	x	x	
Urine sample for dipstick analysis and pregnancy testing for females	x				
Patient pain diary dispensed	x	x			
Prohibited medication ceased	x				
Breakthrough analgesia: Paracetamol prescribed 1g 4-6 hourly	x				

Study medication dispensed: Oral codeine30 mg 4 hourly		X			

b. Primary Study Endpoints

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 be a patient who does not display a reduction in pain scores of **30% or more** over the course of 5 days (as measured on daily pain rating scale).

c. Secondary Study Endpoints

Secondary end points will be the correlations between:

- genotype and clinical response to codeine
- urine metabolites and clinical response to codeine,
- genotype, and urine metabolites.
- m-BPI-sf, SF-8 and Global Impression of Change, and clinical response to codeine and genetic group.

4. Subject Selection and Withdrawal

a. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the trial:-

I. Male or female Caucasian subjects, ages between 18-80 years.

II. Signed and dated written informed consent.

III. Females of childbearing potential must have a negative pregnancy test and be practicing an effective form of contraception.

IV. Patients with a chronic pain condition greater than 3 months duration that has been diagnosed by a pain management specialist.

V. Patients with moderate to severe chronic pain (defined as a score of 4 (out of 10) or above on worst pain in the last 24 hours (question 3) on the Brief Pain Inventory at screening and daily in the Patient Diary during pre-treatment.)

VI. Adequate renal function (serum creatinine females <130 μmol/l: males <150 μmol/l).

VII. Liver enzymes (AST or ALT) less than twice the upper limit of normal. Alkaline phosphates less than twice the upper limit of normal.

VIII. Bilirubin within the normal range, or abnormalities clinically insignificant in the judgment of the investigator.

IX. Deemed capable of complying with study schedule, procedures and medications.

b. Exclusion Criteria

I. Patients with a known sensitivity to codeine or who have a history of experiencing intolerable opioid analgesic side effects.

II. Patients whose pain could be adequately controlled by increasing their dose of weak opioids.

III. Patients with a history of recreational drug use within the last 2 years.

IV. Patients with a history of alcohol abuse within the last 2 years.

V. Female patients who are pregnant, lactating or of child bearing potential who are not taking adequate contraceptive precautions i.e. an oral contraceptive, an approved hormonal implant, an intrauterine device or condoms/diaphragm and spermicide). A woman of childbearing potential is defined as any female who is less than 2 years post-menopausal or has not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).

VI. Abnormal serum electrolytes, which in the investigators opinion would exclude the patient from this study

VII. Abnormal urine analysis, which in the investigators opinion would exclude the patient from this study

VIII. Hemoglobin outside the normal limits and white blood cell count below the lower limit of normal or above 12 x 10^9/l.

IX. Concurrent surgery, radiotherapy, chemotherapy or nerve blocks and those who have received this treatment 4 weeks prior to the study.

X. Patients taking drugs known to be inhibitors of the cytochrome P450 isozyme 2D6 who are unable to cease taking their medication for the study period (Appendix 4).

XI. Patients taking medications that would interfere with the urinalysis e.g. morphine, hydromorphone.

XII. Patients who have anxiety or the depression of a degree that the investigators judge that participation in the study would be detrimental to their mental health.

XIII. Patients who are unable to understand and complete assessment questionnaires in English.

XIV. Patients who have been in another clinical study within the last 4 weeks.

c. Subject Recruitment and Screening

Patients who fulfill the main inclusion / exclusion criteria will be identified from the chronic pain clinic database and approached either at a clinic review or via postal invite to participate in the study. If approached in the chronic pain clinic the investigator will discuss the study with the patient and a research nurse will provide a Patient Information Sheet (Appendix 1) for them to take home and read.

If approached by postal invite the research nurse will send a Patient Information Sheet to the subject and will contact them via telephone approximately 3-5 days later to explain the study and answer questions so that the patient can make an informed decision to take part in the study. Patients who are willing to take part in the study will attend the research chronic pain clinic for a screening visit approximately 1 week following the patient information sheet and invitation to join the study. The investigator or co-investigator will obtain informed consent prior to any study related procedures taking place at the screening visit. All stages of the consent process will be clearly documented in the trial subject's medical notes, which will clearly identify the subject taking part in a clinical trial. Once informed consent has been given the patient will be allocated a Unique Subject Identification numbers and their details will be recorded on a subject Recruitment Log which will be stored in the Trial Master File.

The patient's medical notes will detail the patient's participation in this study and a copy of the patients consent form and Patient information sheet will also be filed in the Patients Medical Records. A copy of the research notes taken at each visit will also be stored in the patient's medical records along with any correspondence to the GP or the Patient in relation to the study.

d. Withdrawal of Subjects

Patients may withdraw at any time and for any reason (or without giving a reason). Data will be collected up until the time of the patient's withdrawal from the study.

The investigator may withdraw the patient from the study at any time. Reasons for removing a subject from the study include, but are not limited to:

- Adverse events
- Violation of the protocol
- In the patient's best interests

Patients will have a contact number for an investigator in case of late toxicity or side effects. All patients will be followed up and reviewed regularly in the outpatient department. In addition the patient's GP will be informed by the research nurse of the patient's participation in the study following the screening visit and will have a contact number for the investigator.

In the cases of patient withdrawal due to reasons other than toxicity or lack of efficacy, additional patients will be recruited until the target number of patients is achieved. Such patients will be given the next available study number.

The primary reason for withdrawal will be documented as one of the following: adverse events, violation of the protocol, lack of efficacy, lost to follow-up, withdrawal of consent, death or other. The investigator will make reasonable attempts to contact patients who are lost to follow-up e.g. 2 phone calls and a letter.

All serious adverse events, and those which cause premature withdrawal of the subject from the study, that have not resolved by the end of the study, will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change. This may involve the subject making additional visits to the centre.

5. Study Drug

a. Description of Investigational Medicinal Product (IMP)

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. There will be sufficient supplies for 150 patients.

Preparation	Patients	Dose	Form
Codeine Phosphate	150	30mg	Tablet

b. Product Sourcing Manufacture and Supply

The Codeine Phosphate Tablets 30mg will be purchased by the Pharmacy Dept LTH from Phoenix H/C Distribution. They are manufactured by TEVA UK. Ltd and have a Manufacturers Authorization PL0289/506IR.

The product will be stored and dispensed from a Pharmacy located within the Leeds Teaching Hospital Trust. The product will be stored in a secure dry place, protected from light and below 25^{o}C. The product will contain an expiry date.

c. Method for Assigning Subjects to Treatment Groups

Patients will be enrolled in sequential order i.e. 01, 02, 03 etc. Each patient will receive codeine phosphate at 30mg every four hours for 5 days.

d. Preparation and Administration of Study Drug

Drug supplies will be received and processed by the clinical trials pharmacist at a suitably located Pharmacy within Leeds Teaching Hospital Trust. Study medication will be held under the supervision of the clinical trials pharmacist and codeine phosphate is a Schedule 5 controlled drug it will be stored in a locked drug cabinet at a cool temperature, protected from light. The clinical trials pharmacist will be issued with a trial specific pharmacy site file which will contain all pharmacy related documents for the study. The clinical trials pharmacist will be responsible for completing both the study drug accountability logs and daily recording of the minimum/maximum temperature of the drug cabinet where the study medication will be stored.

A request form will be completed by the investigator when a patient is eligible to commence the treatment (visit 2). Dispensing will be recorded in a drug dispensing log held by the pharmacist in the pharmacy site file.

All used, unused and returned trial medication/packaging which has been dispensed will be returned to Pharmacy for drug accountability and controlled destruction.

e. Subject Compliance Monitoring

Patients will be issued with a trial diary to record the date, time and dose of study medication taken. This will be reviewed by the research nurses to ensure the patient has taken the study medication as instructed. If a patient has not been compliant with the study medication the investigator may decide to withdraw them from the study as described in section 4.4.

f. Prior and Concomitant Therapy

Patients will stop all prohibited medications listed in appendix 18.4 at the screening visit (visit 1). Patients will be allowed to continue with their prescribed antidepressant, anticonvulsant or non-steroidal anti-inflammatory (NSAID) medication providing the treatment was initiated at least 2 weeks prior to commencing the study, does not induce the CYP2D6 enzyme and is at a stable dose. All concomitant medication and any changes therein will be recorded in the case record file (CRF). Patients should not commence any new drug therapy throughout the codeine treatment period.

g. Non IMP Breakthrough Analgesia (NIMP)

The patient will be dispensed 64 paracetamol tablets (500mg) as breakthrough analgesia. The patient will be instructed by the research nurse to take 1000mg 4-6 hourly (maximum of 4g in 24 hours) if their pain becomes unacceptable to them during this period and to record the amount, date and time breakthrough analgesia in their trial diary cards.

h. Packaging

Codeine Phosphate 30mg Tablets will be provided as open label commercial stock of 28 tablets per pack. Each pack will be labeled with Annex 13 compliant label, directions for use, spaces for Patient Initials, Patient Number, sponsor name, sponsor ID number and Date of Dispensing.

Paracetamol 500mg tablets will be provided as open label commercial stock of 32 tablets per pack. Each pack will be labeled with Annex 13 compliant label, directions for use, spaces for Patient Initials, Patient Number and Date of Dispensing.

i. Receiving, Storage, Dispensing and Return

Receipt of Drug Supplies

All drug supplies (IMP & NIMP) will be securely delivered to the allocated Pharmacy Department within The Leeds Teaching Hospitals NHS Trust. Where they will be received and checked by the Pharmacy Clinical Trials Team

Storage

As codeine phosphate is a Schedule 5 controlled drug it will be stored in a locked drug cabinet and at a cool temperature <25^{o}C, protected from light.

Dispensing of Study Drug

A request form will be completed by the investigator when a patient is eligible to commence the treatment (visit 2). Dispensing will be recorded in a drug dispensing log held by the pharmacist in the pharmacy site file.

Return or Destruction of Study Drug

All used, unused and returned trial medication/packaging which has been dispensed will be returned to Pharmacy for drug accountability and controlled destruction.

All returned medication will be counted and recorded on individual patient accountability records. It will be retained in pharmacy until authorization is received from the sponsor to destroy it. Destruction will be by incineration by White Rose Environmental according to the LTH Trust Destruction Standard Operating Procedure.

6. Laboratory Assays

a. Clinical Chemistry and Hematology

Maximum venous blood sample of 20 mls will be collected at the screening visit (visit 1) for clinical chemistry and hematology (to include electrolytes, serum creatinine, AST/ALT, alkaline phosphatase, bilirubin, haemoglobin, white blood cell count). This will be done in accordance with the Leeds Teaching Hospital NHS Trust policy and practice guidelines.

b. Urinalysis

A urine sample will be collected in a plain sterile container for dipstick urine analysis using Combur Test® reactive strips to ensure there are no underlying medical conditions that require further investigation. The reactive strips document the specific gravity and Ph of the urine as well as the presence of leukocytes, nitrates, protein, glucose, ketones, urobilinogen, billrubin and blood.

Female patients of childbearing potential will be required to take a urine pregnancy test.

c. Cytochrome P450 Genotyping

Cytochrome P450 genotyping allows the determination of DNA sequence polymorphisms in certain human genes (P450 genes) which are associated with the metabolism of both natural and extraneous products. The effect of these genes regulates the amount of active pharmaceutical substance in the circulation of patients.

Although there are many P450 genes, three major types are responsible for the metabolism of most commonly used drugs and the one responsible for codeine metabolism is called 2D6. Because the 2D6 gene is highly polymorphic and varies greatly between individuals this leads to great variability in the way that individual patients respond to codeine-based drugs. According to the particular 2D6 alleles that an individual possesses, they can be classified as poor
Metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra metabolizers (UMs), and correspond to very low, low, normal and high 2D6 enzyme activity respectively [12]. Individuals are placed into one of these categories based on a direct assay of their enzymatic activity rather than their genotype for CYP2D6 [12].

CYP450 2D6 genotyping is now simply performed using the validated, simple, patient friendly, non-invasive Oragene•DNA Self-Collection Kit. The kit is an all-in-one system for the collection, preservation, transportation and purification of DNA from saliva. The patient's genetic material is chemically extracted and the 2D6 genotype determined. The analysis will provide information on the nature of each of the 2D6 alleles that any individual possesses. The nature of these alleles indicates how that individual is likely to clinically benefit from the use of codeine.

The patient will be instructed on how to use the collection kit by the research nurse. They will be asked to supply a 2ml saliva sample directly into the collection kit. Samples will be identifiable by the subject's trial number, initials, date of sample and stored within the pain clinic at Seacroft Hospital at room temperature. Samples will be transported in batches to KBiosciences Laboratory, Hertfordshire UK where they will be analyzed.

d. Urine testing for the products of Codeine Metabolism

In the human liver codeine, which is chemically methyl-morphine, undergoes glucuronidation to generate codeine-6-glucuronide, N-demethylation mediated by another cytochrome P450 enzyme, 3A4 to generate the inactive norcodeine metabolite and O-demethylation mediated by cytochrome P450 2D6 to morphine. Codeine itself is effectively a pro-drug, with little or no intrinsic analgesic action. Morphine is further metabolised by hepatic glucuronidation to yield the conjugates morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G). The extent of the ability of an individual to metabolise (demethylate) codeine can be simply detected by analysing a urine sample before and after 3 days of oral codeine medication. In a 2D6 poor metaboliser the levels of morphine, M-3-G or M-6-G in the urine will be very low or not detected. This is in contrast to the normal (extensive) metaboliser who will have formed the codeine metabolites of morphine, M-3-G or M-6-G more readily, leading to higher levels excreted in the urine.

The urine samples will be collected in sterile universal containers identifiable by the subjects trial number, initials, date of sample and stored within the pain clinic at Seacroft Hospital at -20 ^{o}C. Samples will be transported in batches and analyzed using an automated validated bioanalytical assay incorporating liquid chromatography with tandem mass spectroscopy (LC-MS/MS). The assays will be performed at Leeds Teaching Hospital Trust which is an ICH good laboratory practice (GLP) – compliant facility. The lower limit of quantification (LLQ) for codeine metabolites using this technique is 10ng/ml, which should be sufficient for the purpose described.

A correlation will be made between the patient's urine metabolic profile and that of their genotyping. This may be used to determine whether in future a single cost-effective test of urine,or genotyping will be sufficient.

7. Study Procedures

a. Visit 1

Following the patient giving informed consent (appendix 3) the following assessments and procedures will be conducted at visit 1 (screening visit) to check the patient's eligibility for the study:

- Demography including ethnicity
- Pain assessment via m-BPI-sf, SLANSS, SF-8 (appendix 5 to 8)
- Vital signs of blood pressure and pulse (recorded using a Dinamap Machine for accuracy) and respiratory rate will be recorded by the research nurse to rule out any possible health conditions that may be detrimental to the participant if they entered the study.
- Medical history
- Current and past medical conditions
- Concomitant medications
- Blood sample for clinical chemistry and haematology
- Urine sample for dipstick urine analysis and for pregnancy test (female patients of childbearing potential only)

Eligible patients will cease to take any prohibited analgesic medications (appendix 18.4) at this visit. They will be dispensed Paracetamol as breakthrough / rescue medication and instructed to record the date, time and amount taken in the patient diary. Full instructions on how to complete the patient diary will be given by the research nurse to each patient.

All screening and pre-treatment assessments will be recorded in a screening booklet separate to the full Case Report Form (CRF). At this stage patients will be identified by their initials and date of birth (e.g. ABC 01/01/61). If a patient is then entered to the study, the screening booklet will be attached to the full CRF and each page will be labeled with the patient number.

A standard letter will be sent to the patient's GP by the research nurse notifying him/her of the patient's consent to participate in the study immediately following the screening visit.

b. Visit 2

At the end of the pre-treatment period the patient will attend the pain research clinic for the visit 2 (treatment period) subject to continuing to meet the inclusion/exclusion criteria. The patient's vital signs of blood pressure, pulse and respiratory rate will be recorded by the research nurse.

Changes in concomitant medication will be documented and the patient will be asked open questions to ascertain adverse events if any.

At this visit patients will be asked to provide a urine sample for codeine metabolites.

The patient will also be asked to supply a saliva sample for genetic testing of the CYP2D6 gene. Eligible participants will then be dispensed a 5 day blister pack containing 28 tablets of 30mg codeine phosphate with full instruction on how to take the study medication by the research nurses. The participant will then take the first dose of codeine whilst in clinic.

Patients will complete a daily assessment in their patient diary at home as well as recording the date, time and dose of study medication and any breakthrough analgesia taken. The patient will rate his/her daily pain before retiring to bed by completing the Modified Brief Pain Inventory-Short Form (m-BPI-sf) as shown by the research nurse.

Patients will be allowed to continue to take breakthrough/rescue doses of paracetamol for pain relief when necessary throughout the treatment period which will be recorded by the participant in the patient diary. On the day prior to the scheduled visit 3 participants will be requested to obtain an early morning urine sample in a universal collection vial supplied at visit 2 for opioid metabolities. This may be kept until visit 3 in a cool environment. This is to allow analysis of drug and metabolites levels at a time when the participant is well equilibrated with codeine and prevent a false result if only a post treatment urine test was utilized as codeine and metabolites will be falling and the discriminatory power of these measurements may start to decrease.

c. Visit 3

At the end of the treatment period the patient will attend the pain research clinic for the visit 3 (end of treatment). Changes in concomitant medication will be documented and the patient will be asked open questions to ascertain adverse events if any (Have you had any symptoms or complaints since you received the test treatment/since I last asked you?).

The patient will complete the pain questionnaires m-BPI-sf and the SF-8 followed by the patient and investigator making an assessment of their global impression of change (Appendix 5 – 8).

At this visit patients will be asked to provide another urine sample for opioid metabolites for repeat testing.

At this visit patients will cease to take codeine phosphate and paracetamol breakthrough/rescue medication and will recommence their previous analgesic medication. All blister packs used and un-used medication will be returned to the Pharmacy.

d. Follow up Telephone Call

The research nurse will contact the patient by telephone 7 days after visit 3 to check the patients well-being and any possible late adverse events. This will be recorded in the patient's medical notes and CRF.

8. Statistical Plan

The proportion of codeine non-responders will be estimated. Logistic regression will be used with genetic group and levels of codeine metabolites as predictors of the non-responders.

a. Sample Size Determination

A sample size of 121 subjects will give 90% power to detect a larger proportion of codeine non-responders than the null hypothesis of 10%, assuming the true proportion is 20%, using a 5% significance level for a 1-sided test.

A drop-out rate of 20% is assumed thus implying recruiting 150 subjects will give 121 evaluable subjects.

b. Statistical Methods

Primary Analyses

The primary endpoint is the patient's status as a codeine responder or non-responder. The overall population estimate of the proportion of responders will be estimated and 95% confidence intervals will be produced using the exact binomial distribution.

The responder/non-responder status will be tabulated against the four genetic groups. Logistic regression will be used to formally compare the proportions.

The log-transformed levels of the six codeine metabolites measured in urinalysis will be summarized for responders and non-responders, and also for the four genetic groups and oral fluid, using means, SDs, medians and range and using box-and-whisker plots. ANOVA will be used on each log-transformed metabolite to compare the four genetic groups.

Logistic regression will be used with the log-transformed levels of the metabolites as covariates to predict the responder/non-responder status.

A multivariate logistic regression model that combines the genetic group and the log-transformed metabolite levels to predict responder/non-responder status will be fitted. The suitability of the model as predictor of responder/non-responder status will be assessed using ROC curves.

Secondary Analyses

The secondary endpoints, m-BPI-sf, SLANSS, SF-8 and Global Impression of Change, will be summarized by responder/non-responder status and by genetic group in terms of means, SDs, median and range.

Subject Population(s) for Analysis:

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- Enrolled population: Any subject who attended the screening visit.

- ITT population: Any subject who attend three visits and thus had their genetic group determined and the primary endpoint was observed.

- Per-Protocol population: Any subject who attended all three visits and underwent the telephone follow-up and received the protocol required study drug exposure.

9. Pharmacovigilance: Safety and Adverse Events

a. Defining of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient during or following administration of an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the trial drugs, whether or not considered related to the trial drugs. All Adverse events will be assessed regarding their relationship to both IMP and NIMP.

All clearly related signs, symptoms, and abnormal diagnostic procedures or results will be recorded in the source document, and grouped under one diagnosis. All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The most likely side effects to be observed with oral Codeine Phosphate as per the Summary of Products Characteristics (Appendix 9) include dizziness, dysphoria, sedation, constipation, sweating, itching, nausea, vomiting, drowsiness, dry mouth, miosis, orthostatic hypotension, urinary retention and constipation.

b. Defining Serious Adverse Events (SAEs)

A Serious Adverse Event is defined in general as an untoward (unfavourable) event, which:

- Is fatal. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.
- is life-threatening
- requires or prolongs hospitalisation

- results in persistent or significant disability or incapacity
- is a congenital anomaly or a birth defect, or
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above
- Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the investigator requires reporting.

c. Defining Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs assigned by the local investigator as both *suspected* to be related to the trial drugs and *unexpected* are subject to expedited reporting. An event is unexpected when information is not consistent with the available product information or if they add significant information on the specificity or severity of an expected reaction.

d. Reporting AEs

AEs will be collected for all patients and will be evaluated for duration and intensity according to the NCRI Common Toxicity Criteria.

AEs will be collected for all patients from first dose of protocol treatment until 30 days after the last dose of treatment with a protocol IMP.

Information about AEs, whether volunteered by the patient, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the CRF.

A copy of all reported AEs will be sent to the sponsor if requested.

e. Reporting SAEs

SAEs will be collected for all patients from first dose of protocol treatment until 30 days after the last dose of treatment with a protocol IMP.

All investigators should refer to the Summary of Product Characteristics (SPC) Brochure when determining whether a SAE is expected.

SAE must be reported on a sponsor approved SAE form and faxed through to the Sponsor QA Office on 0113 – 39 26397, within 24 hours of any member of the research team becoming aware of the SAE.

f. Reporting SUSARs

All SAEs assigned by the local investigator as both suspected to be related to protocol-treatment and unexpected will be reviewed by the Chief Investigator (CI).

Such SAEs will be classified as SUSARs and will be subject to expedited reporting to the REC and MHRA.

All SUSARs occurring whilst on trial (until 30 days after the last day of the last treatment) must be reported on a sponsor approved SAE form and faxed through to the trial office / Sponsor QA, within 24 hours of any member of the research team becoming aware of the SUSAR.

The CI will inform the MHRA ①, the Main Research Ethics Committee (Main REC) ① and the Sponsor ② of SUSARs within the required expedited reporting timescales.

① SUSARs must be reported to the REC / MHRA within 7 calendar days of the CI (or their research team) being informed of the event, if they result in Death or are deemed to be life-threatening. Follow-up information must be reported within 8 calendar days.

① Any SUSARs not resulting in Death or deemed to be life-threatening must be reported to the REC / MHRA within 15 Calendar days of the CI (or their research team) being informed of the event. Follow-up information must be reported within 8 calendar days.

② All SUSARs must be reported to the sponsor QA office (on 0113 – 39 26397) within 24 hours of the event being reported to the CI (or their research team).

g. Pregnancy

If a patient is found to be pregnant whilst taking part in the study the investigator must promptly notify The Leeds Teaching Hospitals via the Research and Development office, withdraw patient from the study, perform study completion assessments and collect details of due date. The event will be reported as an SAE.

Pregnancy follow-up will be conducted by the investigator as part of their drug safety monitoring responsibilities and will not form part of the study dataset. All follow up information collected will be forwarded to the sponsor with a final report to be issued to the Ethics Review Committee.

h. Annual Safety Report (ASR)

An ASR must be submitted to the main REC, MHRA and the Sponsor on the anniversary of the Clinical Trial Authorisation being granted. The CI must review and sign / date the report.

10. Data Handling and Record Keeping

a. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Calldicott Guardian, The Research Governance Framework for Health and Social Care and Ethics Committee Approval.

Patients will be identified by their initials, date of birth and patient number only which will be made available to study monitors/auditors/inspectors from regulatory authorities as well as those involved in the care of the patient. All investigators will maintain confidentiality as outlined in the Data Protection Act (1998).

b. Source Documents

Patient records and other source data must be kept for the maximum period of time permitted by the hospital but not less than 15 years. The data retained in the hospital medical records for each patient should contain the following information:

- study number , brief description or title of study date that the subject gave written consent
- all visit dates
- all adverse events
- all concomitant medications

On-site monitoring will also include source document verification (SDV). SDV is the procedure whereby the data contained in the case report forms (CRFs) are compared with the primary source data (e.g. patient notes, original recordings from automated instruments, X-ray films, ECG tracings, laboratory results) contained in the subject records held at the investigational site, and thereby verified as accurate.

The Investigator must be aware that:

- SDV is a part of the normal monitoring process. It will be carried out by designated study personnel (LTHT staff) and will be done in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements.
- SDV will be carried out by direct comparison of entries made in the CRF with appropriate source data. Direct access to source data requires that the subject gives written, documented consent to this.
- The following information will be verified from source documents for all subjects:
- Subject identity – date of birth, sex, initials and subject number
- Primary efficacy variable or data from which it is derived (if possible)
- Diagnosis of the condition under investigation and other selected eligibility criteria
- Details of serious adverse events
- Verification of additional items will be decided on a study-specific and site-specific basis and will be confirmed in the SDV Plan.

c. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for this study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct the error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE ERRORS by any method. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. Never use correction fluid. The Investigator must review all entries for completeness and correctness.

The Investigator is responsible for the quality of the data recorded in the case report form. The data recorded should be a complete and an accurate account of the subject’s record collected during the study.

The Investigator agrees to complete and sign the case report forms in a timely fashion after completion of each subject and make them available to the study monitor for full inspection. In addition, any data queries prepared after the original case report form has been completed should be answered promptly.

The study monitor (a dedicated person from the Pain Management Research team) will review the case report forms for completeness and adherence to the protocol.

d. Records Retention

The Investigator will retain essential documents until 15 years post study. These will be stored in a locked room with limited access (research team members only) on D ward, Old Day Unit Seacroft Hospital Leeds. The items will be stored in a clearly labeled storage box stating study name, funder/sponsor details, storage and destruction date.

Records to be retained by the Investigator include, but are not restricted to the following:

- Signed and dated study protocol and amendments
- SPC of the IMP and NIMP
- Investigator agreement.

- Signed and dated informed consent documents.
- Application(s) to ethics committee/ institutional review board Ethics committee
- Ethics committee composition.
- Regulatory authorisation (if appropriate)
- Curriculum vitae of the Investigator and personnel to whom he/she has delegated some of his/her responsibilities as an Investigator.
- All clinical laboratory normal ranges in place during the study (if appropriate).
- Clinical laboratory accreditation certificate or certification of established QC and/or external QA or other validations (if appropriate).
- Details of study material/supplies shipment dates, batch numbers, method of shipping etc.
- Treatment allocation.
- Study initiation report.
- Monitoring log.
- Case report forms.
- Serious adverse event reports.

e. Quality Assurance

The Sponsor has systems in place to ensure that there is reporting and appropriate action taken in respect of:

(a) Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.
(b) Urgent safety Measures
(c) Protocol violations

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or
(b) The scientific value of the trial.

Investigators will promptly notify the Sponsor QA Office of the following within the required timeframe, once they become aware of:

(a) Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation.
(b) Urgent safety Measures
(c) Protocol violations
(d) Any amendments to the trial
(e) Any changes the Clinical Trial Risk Assessment (form A).
(f) Any other issues as stated in the Research Sponsorship Agreement (RSA)

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the RSA.

11. Study Monitoring, Auditing, and Inspecting

a. Study Monitoring Plan

The investigator will permit study-related monitoring, audits and inspections by the Ethics Committee, the Sponsor, Regulatory Authority and the sponsor. This study will be monitored by the Project Manager for Pain Research. In line with the responsibilities set out in the Research Governance Framework and Directive 2001/20/EC (if applicable) the Investigator will ensure that the sponsor or other regulatory monitoring authority is given access to all study-related documents and study related facilities.

Participation as an investigator in this study implies adherence to the principles and responsibilities of the Research Governance Framework, ICH/GCP and Directive 2001/20/EC.

12. Ethical Considerations

This study will be conducted according to the standards of International Conference on Harmonization Good Clinical Practice Guideline, Research Ethics Committee regulations, EU Clinical Trial Directive (if applicable) and any applicable government regulations and Leeds Teaching Hospitals NHS Trust Research Office policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Ethics Committee (REC) for approval of the study conduct. The decision of the REC concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided with an information sheet describing the elements of this study and sufficient information for subjects to make an informed decision about their participation in this study. See Appendix 18.2 for a copy of the Information Sheet. The subject will complete and sign a consent form to indicate that they are giving valid consent to participate (See Appendix 18.3). This Information Sheet and Consent form will be submitted with the protocol for review and approval by the REC for the study.

13. Study Finances

a. Funding Source

This study is financed through an educational grant from NAPP Pharmaceuticals.

b. Subject Payments

Patients will not receive payment for participating in this study. However the patients travel expenses will be paid during the study for study related visits.

14. Sponsorship

The Leeds Teaching Hospital Trust is the sponsor for this study.

15. Statement of Indemnity

Clinical negligence indemnification will rest with the participating NHS Trust (The Leeds Teaching Hospitals NHS Trust) under standard NHS arrangements. As sponsor, the Trust does not provide indemnification against claims arising from non-negligent harm.

16. Publication Plan

Findings from the study will be published in professional and academic journals and presented at relevant local, national and international conference. Findings from this study will be written up as part of a PhD thesis.

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15.2 PARTICIPANT INFORMATION SHEET

PARTICIPANT INFORMATION SHEET

A study to investigate the prevalence and genetic profile of patients with chronic pain who do not respond to codeine medication

We would like to invite you to take part in a research study. Before you decide to take part you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

(Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study).

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Part 1:

What is the purpose of the study?

Codeine is a pain killer that is widely used to relieve moderate to severe pain. We know that codeine is successful in relieving pain in the majority of people, however a small number of people find that codeine is not effective in relieving their pain. It has been estimated that around 1 in every 10 patients does not get adequate pain relief from codeine medication, and these patients are called non-responders. We are interested to know how many patients attending a specialist pain clinic do not respond to codeine.

Why have I been invited?

Your doctor has referred you to this pain clinic to help with your pain control. At the moment a painkiller that is commonly used for your type of pain is codeine. We are conducting this study

to better understand why some people with chronic pain do not respond to codeine and we would like to invite you to take part. We plan to complete the study in 150 patients.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you withdraw from this study your blood and urine samples will be destroyed.

What will happen to me if I take part?

You would be involved in the study for about 15 days and have to visit the hospital 3 times. You will have to keep a diary (which will be provided for you) of when you take the codeine and/or paracetamol during the study. You will be asked to provide a total of one blood sample, one saliva sample and 4 urine samples during the study. You will also be asked to refrain from taking the following during the study period as these can affect the tests we are conducting: poppy seeds, grapefruit juice and any other medication which contain codeine.

Expenses and payments:

Transport will be provided for you either as a taxi (the cost will be met by the study group) or if you use your own car then you will be reimbursed at a reasonable mileage rate.

What do I have to do?

VISIT 1: This visit will last about 1 hour. You will be assessed by a doctor and a research nurse to see if you are suitable to take part. You will have sufficient time to make up your mind as to whether or not you wish to participate in the study. If you decide that you would like to take part in this study you will be asked to sign an Informed Consent Form to say that you agree to take part. You will be interviewed about your current condition and medication, as well as other conditions or medications used in the past (your medical history). You will be asked to refrain from taking food containing poppy seeds and grapefruit juice until you have completed the study. Additionally, you will be asked to fill in questionnaires about your current pain condition. We will collect a urine sample and take a blood sample which will be tested to check your general health. Your current painkillers and medication will be reviewed and you may be asked

to stop taking some types of painkillers during this study. The research team will inform you of any medications that you will need to stop taking. You will be provided with paracetamol to take home if any pain medication is stopped at this visit. You will also be given a diary to take home with you so you can record when you take any medication.

VISIT 2: This will be 2 days after visit 1 and will take approximately 30 minutes**.** At this visit you will be asked to provide a saliva sample. This is done by spitting into a collection pot until 2mls (1/2 teaspoon) is collected. The saliva will contain some of the cells lining the inside of your cheek, and this will be used to extract DNA which contains your genetic information about your response to codeine. At this visit you will commenced on a 5 day course of codeine tablets, 1 tablet (30mg) every 4 hours as treatment for your pain. You will take your first dose at the clinic and we will ask you to provide another urine sample. This test is to see how much of the drug is in your body and we will be able to test your response to codeine. You will also be asked to complete some questionnaires about your pain and you will be given paracetamol to take home as an extra pain killer if you should need it. You will be given a diary card to take home with you so you can record each time you take your codeine or paracetamol.

DAY 4: We would like you to collect an early morning urine sample in a container provided at visit 2. This can be kept in a cool place overnight and brought to clinic the following morning when you attend for visit 3.

VISIT 3: Will be 5 days after visit 2 and will last for 30 minutes. You will be asked about your pain and any side effects that you have experienced since you have been taking codeine. At this visit you will be asked to complete questionnaires about your pain (same as previous visits) and to rate the effectiveness of the codeine tablets for your pain. At this visit you will be asked to provide your final urine sample to test how your body handles codeine. The research team will keep in regular telephone contact with you during the study. If you wish to contact any member of the research team for advice then you may do so at any time. We would like to know if at any point your pain becomes uncontrolled and if you develop any side effects. If you find that your pain does not respond to the codeine or that you develop intolerable side effects at any point, then you may be switched on to an alternative medication for pain. This may involve addition visits to the Research Pain Clinic to the 3 planed visits stated. Seven days after visit 3 you will be telephoned by the study nurse just to check that you are well and to ask about side effects if any.

What is the drug that is being tested?

Codeine is a painkiller for treating moderate pain that has been available for many years around the world. In England it is available on prescription and is similar in strength to Tramadol.

What are the alternatives for diagnosis or treatment?

The type of pain you have can be difficult to treat. There are a number of drugs that doctors may try to treat this type of pain but these do not work in all patients. You can discuss alternative treatments with your Pain Clinic Consultant or GP.

What are the possible disadvantages and risks of taking part?

You may find giving a blood sample uncomfortable and this may result in slight bruising. There are no other known risks involved in taking part in this study. If you have private medical insurance you should check with the company before agreeing to take part in this study. If during the course of this study your doctor finds out anything about your health which you do not already know, you will be told and we will inform your GP.

Women of childbearing potential must have a urine pregnancy test performed and their participation in the study will only be permitted if they agree to practice acknowledged highly effective contraceptive measures throughout the study (e.g. sterilisation, contraceptive implants or injections, coil, oral contraceptives (i.e. the pill), practicing sexual abstinence or a partner who has had a vasectomy). Codeine is not contraindicated in women who are pregnant or breastfeeding but they are excluded from participation in this study because it is the research team's policy. Your study doctor will be prepared to answer any of your questions concerning contraception or counsel you accordingly. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor.

What are the side effects?

Like all medicines, the study medication may cause side effects in some patients. Common side effects of codeine which affect less than 1 in 10 people who take this medication include feeling or being sick, constipation, drowsiness, dizziness, headache dry mouth, sweating, itching and difficulty in passing urine (urinary retention). Most of these side effects tend to occur at the beginning of treatment and usually wear off after several days. If symptoms persist, then it may be necessary to either reduce the dose of codeine or change to an alternative medication.

In addition to those side effects mentioned above, the study drug might cause side effects that no one knows about yet. If you should suffer from any of the side effects listed above or any other symptoms during the study you should report it to your doctor at your next visit or if you become concerned in any way please contact:

Dr Simpson, Suzanne Rogerson (Research Nurse) or Helen Radford (Senior Research Nurse /Project Manager) Telephone number (Hospital): Leeds (0113) 2063131 or 2063132, Mobile: 07786 250784

What are the possible benefits of taking part?

We hope that the codeine treatment that you will be given will help control your pain and cause you no or minimal side effects. However, this cannot be guaranteed. The information that we get from this study will hopefully enable us to find out more about why some people react differently to codeine painkillers and this may benefit people in the future. If you decide not to take part you will still be given alternative pain killers to control your pain if codeine is unsuitable for you.

What happens when the research study stops?

At the end of the study your doctor will discuss options for your future pain relief with you. If your pain has improved, you will continue the treatment that you have been allocated for as long as you need it.

What if something goes wrong?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes Part 1.

If the information in Part 1 has interested you and you are considering taking part, please read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form. Also on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time and without having to give a reason. We will need to use your data up to the time of your withdrawal. It would be in your best interests to return for a check-up and we would also like to use this data with your consent.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (Leeds (0113) 2063131 or 2063132). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital Patient Advice and Liaison Services (PALS) (0113 2067168).

Harm

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. If you remain unhappy and

wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the research team, research ethics committee and sponsor (or sponsor authorised personnel).They may also be looked at by representatives of regulatory authorities and by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty. Your name, however, will not be disclosed outside the hospital. A copy of your consent form will be sent the research and development office of The Leeds Teaching Hospitals NHS trust who are the sponsor for this study.

Involvement of the General Practitioner/Family doctor (GP)

Your study doctor will contact your GP by letter, to inform them of your participation. By signing this consent form, you are agreeing to this process.

What will happen to any samples I give?

The blood sample that will be taken at the Screening Visit is to check your health and ensure that you meet the conditions for the study. Once these results have been obtained the sample will be destroyed.

Will any genetic tests be done?

The saliva sample that you provide will be used for genetic analysis for the purpose of this research trial only and therefore, there are no insurance implications as a result of taking part in this study. The research records that we collect will be anonymous and kept confidential. Your legal rights are not affected by participating in this study and you may withdraw from the study at any point. If you do withdraw from this study your samples will be destroyed.

What will happen to the results of the research study?

This study is being undertaken as part of a Doctorate research programme (PhD). We intend to publish the results in a scientific journal or be presented at a scientific conference and if you are

interested we can let you know when this happens. You will not be identified by name in any report or publication. Should you wish to see the results, or the publication, please ask your researcher.

Who is organising and funding the research?

The research is being sponsored by Leeds Teaching Hospital NHS Trust and the study is being funded by NAPP Pharmaceuticals by an educational grant.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Leeds (West) Research Ethics Committee.

Further information and contact details

1. *General information about research*

The Medical Research Council has a web site with advice about taking part in clinical trials: **www.ctu.mrc.ac.uk/TakePart.asp**

2. *Specific information about this research project.*

Please ask us: Dr Simpson, Suzanne Rogerson (Research Nurse) or Helen Radford (Senior Research Nurse /Project Manager)

Telephone number: **Leeds (0113) 2063131 or 2063132, Mobile: 07786 250784**

3. *Advice as to whether you should participate*.

You could ask your own GP/practice nurse for advice about this or family members.

4*. Who to approach if unhappy with the study.*

Talk to us first and if you are still unhappy please contact the hospital Patient Advice and Liaison Services (PALS) (0113 2067168).

Thank you for considering taking part in this study. If you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep. If you require any further information then please contact the following:

Suzanne Rogerson (Research Sister) / Helen Radford (Senior Research Nurse / Project Manager)

Pain Management Services

D Ward

Seacroft Hospital

York Road

Leeds LS14 6UH

Tel: 0113 2063132 or 0113 2063131

15.3 CONSENT FORM

CONSENT FORM

A study to investigate the prevalence and genetic profile of patients with chronic pain who do not respond to codeine medication

Centre: **Leeds Teaching Hospital NHS Trust**

Study Protocol Number: **A2007N**

Patient Identification Number for this trial:

Name of Chief Investigator: **Dr Karen Simpson**

Contact details for research team: 0113 2063131 or 0113 2063132

Please initial each box

I confirm that I have read and understand the information sheet dated 8th December 201 2011 (Version 2) for the above study and that I have had an opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, and my medical care and legal rights will not be affected	☐
I agree to give a sample of DNA (saliva sample), for research in this project. I understand how the sample will be collected and that giving a sample for this research is voluntary. I understand that should I withdraw from this study my DNA, oral fluid and urine samples will be destroyed.	☐
I understand that my medical records may be looked at by authorised individuals from the Sponsor for the study, the UK Regulatory Authority or the Independent Ethics Committee in order to check that the study is being carried out correctly. I give permission, provided that strict confidentiality is maintained, for these bodies to have access to my medical records for the above study and any further research that may be conducted in relation to it. I also give permission for a copy of my consent form to be sent to the Sponsor for the study	☐
I understand that wherever my personal data is processed, it will be kept accurate, confidential and secure, and will only be used for the purpose for which it was collected. This is in accordance with the UK Data Protection Act 1998	☐
I understand that (my doctor and/or I, as appropriate) will be informed if any of the results of the medical tests done as a part of the research which are important for my health.	☐
I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test.	☐

I agree that my GP and other professionals involved in my medical care may be notified about my participation in this study. ☐

I understand that I will be required to attend the Research Pain Clinic (Seacroft Hospital) at various time points during the course of the study. ☐

I would/would not like to be informed of the results of this study (please delete)

In signing this form, I give my consent to my participation in this study in the manner set out above.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person obtaining consent (If different from Principal Investigator)	Date	Signature
_____	_____	_____
Principal Investigator	Date	Signature

1 copy for Patient, 1 for Principal Investigator, 1 for Hospital Notes, 1 for sponsor

15.4 MHRA APPROVAL LETTER

Safeguarding public health

MHRA

Ms H Radford
LEEDS TEACHING HOSPITALS NHS TRUST
L WARD, SEACROFT HOSPITAL
YORK ROAD
LEEDS
LS14 6UH
UNITED KINGDOM

12/12/2008

Dear Ms H Radford

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our reference:	18166/0220/001-0001
Eudract Number:	2007-006184-70
Product:	Codeine Phosphate Tablets BP 30mg
Protocol number:	PM07/8404

NOTICE OF ACCEPTANCE

I am writing to inform you that the Licensing Authority accepts your request for a clinical trial authorisation (CTA), received on 14/11/2008.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

Amendment 1 (non-substantial) & Amendment 2

Safeguarding public health

MHRA

Ms H Radford
LEEDS TEACHING HOSPITALS NHS TRUST
L WARD, SEACROFT HOSPITAL
YORK ROAD
LEEDS
LS14 6UH
UNITED KINGDOM

14/09/2010

Dear Ms H Radford

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	18166/0220/001-0002
Eudract Number:	2007-006184-70
Product:	Codeine Phosphate Tablets BP 30mg
Protocol number:	PM07/8404
Substantial Amendment Code Number:	Substantial amendment one (12 Feb 2010)

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 17/08/2010.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

Amendment 3:

Safeguarding public health

MHRA

Ms H Radford
LEEDS TEACHING HOSPITALS NHS TRUST
L WARD, SEACROFT HOSPITAL
YORK ROAD
LEEDS
LS14 6UH
UNITED KINGDOM

19/11/2012

Dear Ms H Radford

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	18166/0220/001-0003
Eudract Number:	2007-006184-70
Product:	Codeine Phosphate Tablets BP 30mg
Protocol number:	PM07/8404
Substantial Amendment Code Number:	Code Number: A2007N
Version: 3	
Date: 2012/08/14	

NOTICE OF ACCEPTANCE OF AMENDMENT

I am writing to inform you that the Licensing Authority accepts the proposed amendment to your clinical trial authorisation (CTA), received on 15/10/2012.

This amendment may therefore be made.

You are reminded that where it is appropriate, the Ethics Committee should also be notified of amendments.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

15.5

National Research Ethics Service
Leeds (West) Research Ethics Committee
A/B Floor, Old Site
Leeds General Infirmary
Great George Street
Leeds
LS1 3EX

Telephone: 0113 3923181
Facsimile: 0113 3922863

09 January 2009

Dr Karen Simpson
Consultant Pain Management
Pain Management Services
L Ward Seacroft Hospital
Leeds
LS14 6UH

Dear Dr Simpson

Full title of study:	**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.**
REC reference number:	**08/H1307/132**
Protocol number:	**1**
EudraCT number:	**2007-006184-70**

Thank you for your letter of 22 December 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Study ID card	1	03 October 2008
CV for Helen Radford		03 October 2008
GP/Consultant Information Sheets	1	03 October 2008
Letter of invitation to participant	1	03 October 2008
Sample Diary/Patient Card	1	03 October 2008
Statistician Comments		03 October 2008
Peer Review		18 June 2008
Letter from Sponsor		03 October 2008
Protocol	1	03 October 2008
Investigator CV		28 July 2008
Application		13 October 2008
Response to Request for Further Information		
Participant Consent Form	1.1	22 December 2008
Participant Consent Form: Tracked changes	1.1	22 December 2008
Participant Information Sheet	1.1	22 December 2008
Participant Information Sheet: Tracked changes	1.1	22 December 2008
Reminder letter	1	12 December 2008

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National

Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review –guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H1307/132	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Mr Jon Silcock
Chair

Email: Elaine.hazell@leedsth.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *Site approval form*

Copy to: *Dr D Norfolk*

Clinical Trials Unit, MHRA

Amendment 1:

NHS

National Research Ethics Service

Leeds (West) Research Ethics Committee

Room 22
Floor CD, Block 40
King Edward Home
Leeds General Infirmary
Leeds
LS1 3EX

Tel: 0113 392 6788

15 April 2010

Dr Karen Simpson
Consultant in Anaesthesia & Pain Management
The Leeds Teaching Hospitals NHS Trust
Pain Management L Ward
Seacroft Hospital, York Road, Leeds
LS14 6UH

Dear Dr Simpson

Study title:	**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.**
REC reference:	**08/H1307/132**
Amendment number:	**1**
Amendment date:	**24 March 2010**

The above amendment was reviewed at the meeting of the Sub-Committee held on 15 April 2010.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Advertisement	1.1	12 February 2010
European Commission Notification of Substantial Amendment Form		24 March 2010
Covering Letter		26 March 2010

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

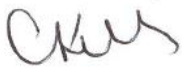
This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H1307/132:	**Please quote this number on all correspondence**

Yours sincerely



Claire Kelly
Committee Assistant Co-ordinator

E-mail: Claire.kelly@leedsth.nhs.uk

Amendment 2:

Health Research Authori

NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Tel: 0113 3050122
Fax: 0113 8556191

04 January 2012

Dr Karen Simpson
Consultant in Anaesthesia & Pain Management
Pallium Research Group
Pain Management L Ward
Seacroft Hospital, York Road, Leeds
LS14 6UH

Dear Dr Simpson

Study title:	**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.**
REC reference:	**08/H1307/132**
Protocol number:	**A2007N**
EudraCT number:	**2007-006184-70**
Amendment number:	
Amendment date:	**12 December 2011**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form	2	08 December 2011
Participant Information Sheet	2 (clean version and tracked changes version)	08 December 2011
Protocol	2 (clean version and tracked	08 December 2011

	changes version)	
European Commission Notification of Substantial Amendment Form		12 Decembe
Covering Letter		09 Decembe

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committee and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H1307/132: Please quote this number on all correspondence

Yours sincerely

p **Dr Rhona Bratt**
Chair

E-mail: Elaine.hazell@nhs.net

Amendment 3:

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Tel: 0113 30 50166
Fax:

29 October 2012

Dr Karen Simpson
Consultant in Anaesthesia & Pain Management
The Leeds Teaching Hospitals NHS Trust
Pallium Research Group
Pain Management L Ward
Seacroft Hospital, York Road, Leeds
LS14 6UH

Dear Dr Simpson

Study title:	**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.**
REC reference:	**08/H1307/132**
Protocol number:	**A2007N**
EudraCT number:	**2007-006184-70**
Amendment number:	**3**
Amendment date:	**14 August 2012**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	3 (clean version and tracked	14 August 2012

	changes version)	
European Commission Notification of Substantial Amendment Form	3	14 August 2012
Covering Letter		20 September 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H1307/132:	**Please quote this number on all correspondence**

Yours sincerely

p.p.

Dr Rhona Bratt
Chair

E-mail: nrescommittee.yorkandhumber-leedswest@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Derek Norfolk, The Leeds Teaching Hospitals NHS Trust*

15.6 PROHIBITED MEDICATION

Prohibited drugs during the study period that would have interfered with the analysis of urinary codeine O-Demethylation (adapted from Palliative Care Formulary (2003) and Flockhart (2007)

SSRI/SNRI's	**Opiates**	**Anti-arrythmics**	**Anti-Psychotics**
Paroxetine Fluoxetine Sertraline Duloxetine Citalopram Fluvoxamine	Morphine Codeine Heroin Hydromorphone Oxycodone Oxymorphone Hydrocodone Fentanyl Methadone	Quinidine Amiodarone Flecainide Propafenone	Haloperidol Thioridazine Chlorpromazine Levomepromazine
Tricyclic/Other Anti-depressants	**Cytotoxic antibiotics**	**Platelet aggregation inhibitors**	**H2 Antagonists**
Doxepin Clomipramine Bupropion	Doxorubicin	Ticlopidine (ADP antagonist)	Cimetidine Ranitidine
Anti-Emetics	**Anti-infectives**	**Anti-Histamines**	**CNS Stimulants**
Metoclopramide	Terbinafine Ritonavir Chloroquine/ Hydroxychoroquine	Chlorphenamine	Cocaine
Cox II Selective inhibitors			
Celecoxib			

15.7 STUDY CASE REPORT FORM

Sponsor: LTHT Study no: A2007N Subject Initials: | | | | | | |

Principal Investigator: Dr Simpson

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.

Patient Notes Study Record

Patient Full Name			
Date of Birth		Date Subject Information Leaflet given to patient	
Date of Informed consent			

Visit 1 , SCREENING DATE:

Sex	
Male	
Female	

Height (cm)	
Weight (Kg)	

VITAL SIGNS:	
Pulse (bpm)	
Resps (per min)	
Blood Pressure	

PRIMARY PAIN DIAGNOSIS: ……..

Duration: ……(years)…… (months)

Date referred to Pain Clinic: ……..

Duration: ……(years)…… (months)

CHILDBEARING POTENTIAL: **YES** ☐ **NO** ☐ **N/A (Male)** ☐

If yes, what contraceptive method used?.....
If no, why?

2 years post menopausal ☐, Surgically sterilized ☐, Other:.....

Urine Pregnancy test: Positive ☐ Negative ☐
(if positive patient is a failed screen)

Has the patient completed the following Questionnaires at this visit:

m-BPI-sf:	**YES** ☐	**NO** ☐
SF 8 :	**YES** ☐	**NO** ☐
SLANSS:	**YES** ☐	**NO** ☐

LABORATORY DATA:

Was blood sample obtained at this visit? Yes ☐ No☐

If No what was the reason?.....

Were the results with in normal range? Yes ☐ No☐

If NO, is there any clinical significance? Yes ☐ No☐

COMMENTS if 'YES':

PREVIOUS & CURRENT DRUG TREATMENT FOR NEUROPATHIC PAIN:

Generic Name	Route	Frequency	Dose	Started	Stopped	On-going

CON-MEDS:
NB check all drugs against prohibited list.

Generic Name	Route	Frequency	Dose	Started	Prohibited ?	Stopped	On-going

Previous Medical History:

Condition	commenced	stopped	ongoing

Urinalysis:

Was a Urinalysis preformed ? Yes ☐ No☐

Test	Result	Abnormal (Y/N)	Clinical Sig? (Y/N)	Comment
Spec. Grav				
PH				
Ketones				
Blood				
Leukocytes				
Nitrates				
Glucose				
protein				

Has the Breakthrough Analgesia been issued with instructions ?

Yes ☐ No☐

Has the patient Diary been issued with instructions? Yes ☐ No☐

Has Patient trial ID card been issued? Yes ☐ No☐

Visit 2: Treatment Visit

Date of Visit:

Does the Participant fulfill the Inclusion / Exclusion Criteria?

Inclusion	**YES**	**NO**
Male or female Caucasian subjects, ages between 18-80 years		
Signed and dated written informed consent		
Females of childbearing potential must have a negative pregnancy test and be practicing an effective form of contraception.		
Patients with a chronic pain condition greater than 3 months duration that has been diagnosed by a pain management specialist.		
Patients with moderate to severe chronic pain (defined as a minimum of 40 mm pain score on the 100mm pain visual analogue scale (VAS) at screening and a minimum average daily pain score of 4 on Daily Pain Rating Scale (DPRS) during pre-treatment		
Adequate renal function (serum creatinine females <130 μmol/l: males <150 μmol/l).		
Liver enzymes (AST or ALT) less than twice the upper limit of normal. Alkaline phosphates less than twice the upper limit of normal.		
Bilirubin within the normal range, or abnormalities clinically insignificant in the judgment of the investigator.		
Deemed capable of complying with study schedule, procedures and medications.		
Exclusion		
Patients with a known sensitivity to codeine or who have a history of experiencing intolerable opioid analgesic side effects.		
Patients whose pain could be adequately controlled by increasing their dose of weak opioids		
Patients with a history of recreational drug use within the last 2 years		
Patients with a history of alcohol abuse within the last 2 years.		
Female patients who are pregnant, lactating or of child bearing potential who are not taking adequate contraceptive precautions i.e. an oral contraceptive, an approved hormonal implant, an intrauterine device or condoms/diaphragm and spermicide). A woman of childbearing potential is defined as any female who is less than 2 years post-menopausal or has		

not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).		
Abnormal serum electrolytes, which in the investigators opinion would exclude the patient from this study		
Abnormal urine analysis, which in the investigators opinion would exclude the patient from this study		
Hemoglobin outside the normal limits and white blood cell count below the lower limit of normal or above 12 x 10^9/l.		
Concurrent surgery, radiotherapy, chemotherapy or nerve blocks and those who have received this treatment 4 weeks prior to the study.		
Patients taking drugs known to be inhibitors of the cytochrome P450 isozyme 2D6 who are unable to cease taking their medication for the study period		
Patients taking medications that would interfere with the urinalysis e.g. morphine, hydromorphone.		
Patients who have anxiety or the depression of a degree that the investigators judge that participation in the study would be detrimental to their mental health.		
Patients who are unable to understand and complete assessment questionnaires in English.		
Patients who have been in another clinical study within the last 4 weeks.		
Does the patient fulfill the inclusion/exclusion criteria?		

NB: any ✔ in a shaded box excludes the patient from study

Give the participant their first dose of Codeine

1st dose Codeine 30mg taken at:

VITAL SIGNS:	
Pulse (bpm)	
Resps (per min)	
Blood Pressure	

Have you reviewed the patient diary for completeness? YES ☐ NO ☐

Comments:

Has the Diary been reissued for the treatment phase? YES ☐ NO ☐

Has the Study medication been issued with instruction? YES ☐ NO ☐

Has the patient been supplied with a urine bottle for Codeine Metabolities to take home for Day 4? YES ☐ NO ☐

Telephone FU Day 4 booked for:……

Time ……..

Researcher Name (print):……

Researcher signature:……

Date:……

TELEPHONE FOLLOW UP VISIT (DAY 4)

Date of Call:

Have there been any AE's: **YES** ☐ **NO** ☐

If YES please record on AE sheet

Have there been any changes to Con Meds? : **YES** ☐ **NO** ☐

If YES please record:

Generic Name	Route	Frequency	Dose	Started	Prohibited ?	Stopped	On-going

Has the patient taken a Urine sample for Codeine Metabolites?

YES ☐ **NO** ☐

Has the patient taken codeine as instructed (ie 30mg QDS)?

YES ☐ **NO** ☐

Remind the patient that the sample needs to be stored in a cool place and brought with them to the next visit along with the study medication, paracetmaol, empty drug packets and their diary.

Next Visit:

Researcher Name (print):……

Researcher signature:……

Date:……

VISIT 3 (END OF STUDY)

Date of Visit:

VITAL SIGNS:	
Pulse (bpm)	
Resps (per min)	
Blood Pressure	

Have there been any AE's: **YES** ☐ **NO** ☐

If YES please record on AE sheet

Have there been any changes to Con Meds? : **YES** ☐ **NO** ☐

If YES please record:

Generic Name	Route	Frequency	Dose	Started	Prohibited ?	Stopped	On-going

Has the patient completed the following Questionnaires at this visit:

m-BPI-sf: **YES** ☐ **NO** ☐

SF 8 : **YES** ☐ **NO** ☐

PGIC: **YES** ☐ **NO** ☐

CGIC: **YES** ☐ **NO** ☐

-
- **Has a Urine sample been obtained for Codeine Metabolites*?**

(*: store at -20c)

YES ☐ **NO** ☐

- **Has the codeine and paracetamol been returned including all empty packaging?** **YES** ☐ **NO** ☐

- **Has the patient returned their Diary?** **YES** ☐ **NO** ☐

- **Is it fully completed?** **YES** ☐ **NO** ☐

If 'No' please comment:

- **Has the patient taken codeine as instructed during the trial period (ie 30mg QDS)?**

YES ☐ **NO** ☐

If No please comment:

If the patient stopped any prohibited medication they may recommence them now.

Telephone FU Day 12 booked for:……

Time ……..

Researcher Name (print):……

Researcher signature:……

Date:……

TELEPHONE FOLLOW UP VISIT (DAY 12)

Date of Call:

Have there been any AE's: **YES** ☐ **NO** ☐

If YES please record on AE sheet

Have there been any other issues? **YES** ☐ **NO** ☐

If 'YES' please comment:

Filing of SDV to Medical Notes:

Has the SDV been copied and filed in the patients Medical Notes?

YES ☐ **NO** ☐

If Yes which volume & section of the medical notes has the SDV been filed to?

Volume:……

Section:……

Researcher Name (print):……

Researcher signature:……

Date:……

15.8 CYP2D6 ALLELE SELECTION & ACTIVITY SCORING SYSTEM

CYP2D6 alleles selected for genotype identification with identification method (tag SNP/deletion/duplication), attributed function and activity score

CYP2D6 Allele	Identification Method	Enzyme Function Level	CYP2D6 Activity Score (Gaedigk *et al*., 1999)[17]
*1	Wild Type (WT) no polymorphisms identified	Normal	1
*1 xN	Duplication	Increased	1xN
*2	SNP: rs16947	Normal	1
*2 xN	Duplication	Increased	1xN
*3	SNP : rs35742686	None	0
*4	SNP: rs1065852 & rs3892097	None	0
*5	Gene Deletion	None	0
*6	SNP: rs5030655	None	0
*9	SNP: rs5030656	Reduced	0.5
*10	SNP: rs1065852	Reduced	0.5
*17	SNP: rs28371706 & rs16947	Reduced	0.5
*41	SNP: rs16947 & rs28371725	Reduced	0.5

Classification of CYP2D6 phenotype inferred from genotype using Gaedigk *et al*., (1999) CYP2D6 activity scoring model (adapted from Crews *et al*. 2012)

CYP2D6 Activity Score (Gaedigk *et al*., 1999)	**Allocation of CYP2D6 phenotype defined by CPIC** (Crews *et al.,* 2012)[32]
0	PM
0.5	IM
1	EM
1.5	EM
2	EM
>2	UM

15.9 CODEINE PHOSPHATE 30MG SMPC

SUMMARY OF PRODUCT CHARACTERISTICS

Codeine Phosphate 30 mg Tablets BP

Version 5

CodeinePhosphate30mgTabletsPL00289_5061Rv5

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Codeine Phosphate 30 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30mg Codeine Phosphate.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.White, biconvex tablets, marked ‘APS’ on one side and ‘30/0508’ on the reverse; or marked ‘APS’ over ‘0508’ on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Codeine phosphate tablets are indicated for the treatment of mild to moderate pain, diarrhoea

and troublesome cough.

4.2. Posology and method of administration

For oral administration. Recommended doses and dosage schedules:

Adults:

Analgesic use:

30-60 mg every four hours when necessary, up to a maximum of 240 mg daily.

Anti-diarrhoeal use:

30 mg three to four times daily.

Anti-tussive use:

15-30 mg three to four times daily.

Children:

Children under 5 years: Not suitable.

Analgesic use: 3 mg/kg bodyweight daily in 4 to 6 divided doses.

Anti-tussive use: 1 to 2 mg/kg bodyweight daily in 4 to 6 divided doses.

The use of cough suppressants containing codeine is not generally recommended in children.

Anti-diarrhoeal use: Not recommended

The Elderly: The adult dosage should be reduced.

4.3. Contra-indications

Codeine phosphate is contra-indicated in patients with hepatic disease, acute respiratory depression, acute alcoholism, acute ulcerative colitis, antibiotic-associated colitis and where there is a risk of paralytic ileus. Codeine phosphate should also be avoided in patients with raised intracranial pressure or with significant head injury (in addition to interfering with respiration, it affects papillary responses vital for neurological assessment).

4.4. Special Warnings and special precautions for use

Codeine is a narcotic analgesic. Tolerance, psychological and physical dependence may occur, especially if large doses are used. Codeine should be avoided in patients with infective diarrhoea, as it may delay the passage of faeces, encourage proliferation of pathogens and mask the severity of the condition. Cough suppression may cause sputum retention, which can be harmful in patients with chronic bronchitis. Use with caution in patients with hypotension, hypothyroidism, prostatic hypertrophy, asthma (avoid during an attack), decreased respiratory reserve and convulsive disorders. Codeine should be avoided, or the dose reduced, in hepatic or renal impairment.

The risk-benefit of continued use should be assessed regularly by the prescriber.

The leaflet will state in a prominent position in the 'before taking' section:

• Do not take for longer than directed by your prescriber.

• Taking codeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.

• Taking a painkiller for headaches too often or for too long can make them worse.

The label will state (To be displayed prominently on outer pack - not boxed):

• Do not take for longer than directed by your prescriber as taking codeine regularly for a long time can lead to addiction.

4.5. Interactions with other medicinal products and other forms of interaction

Codeine may antagonise metoclopramide and delay the absorption of flecainide and mexiletine. It may potentiate hypnotics and anxiolytics. Concurrent administration with monoamineoxidase inhibitors may cause CNS excitation and/or hypertension, and such interactions can occur up to two weeks after stopping the monoamine-oxidase inhibitor therapy. Codeine may also enhance the effects of alcohol. Increased sedation may occur with tricyclic antidepressants. Opioid analgesics may reduce the plasma concentration of ciprofloxacin when taken concomitantly. An enhanced sedative and hypotensive effect may occur if antipsychotics are taken concomitantly with opioid analgesics. The plasma concentration of some opioid analagesics may be increased by ritonavir. Cimetidine may inhibit the metabolism of opioid analgesics. Gastrointestinal effects of metaclopramide and domperidone may be antagonised.

4.6. Pregnancy and lactation

Although there is inadequate evidence of safety in human pregnancy, codeine has been widely used for many years without apparent ill-consequence, and animal studies have not shown any hazard. Codeine is known to be excreted in breast milk, but in amounts too small to be harmful. However, as with all drugs, codeine should be avoided in these conditions unless considered essential by the physician.

4.7. Effects on ability to drive and use machines

Codeine may cause sedation, and patients should be warned not to drive or operate machines if affected.

4.8. Undesirable effects

The most common side-effects of codeine are constipation, respiratory depression, hypotension, urinary retention, drowsiness, nausea, vomiting, headache, vertigo, difficulty with micturition, ureteric or biliary spasm, dry mouth, sweating, facial flushing, bradycardia, tachycardia, palpitations, drowsiness, postural hypotension, hypothermia, hallucinations, dysphoria, moodchanges, miosis, decreased libido or potency, rashes, urticaria and pruritis. Faecal impaction may occur, particularly in the elderly. Such impaction can lead to incontinence, spurious diarrhoea, abdominal pain and rarely colonic obstruction. Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped. Prolonged use of a painkiller for headaches can make them worse.

4.9. Overdose

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Symptoms include central nervous system depression, including respiratory depression, which may develop but is unlikely to be severe unless other sedative agents have been coingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension and tachycardia are possible but unlikely.

Management

This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: RO5D AO4 (opium alkaloids and derivatives)

Codeine produces effects on the CNS and the bowel. These effects include analgesia, drowsiness, mood changes, respiratory depression, decreased gastro-intestinal motility, nausea, vomiting and alterations of the endocrine and autonomic nervous systems.

A major limitation of its clinical use is the potential for development of tolerance and physical dependence in long term use.

5.2. Pharmacokinetic properties

Codeine is readily absorbed from the gastro-intestinal tract. It is metabolised in the liver and excreted mainly in the urine. About 10% of a dose is demethylated to form morphine, which may account for its analgesic effect. Oral availability is approximately 66 %, the plasma halflife is 2.5 to 3 hours with a duration of action of 4 to 6 hours.

5.3. Pre-clinical safety data

Preclinical information has not been included because the safety profile of codeine phosphate has been established after many years of clinical use. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dextrin

Lactose Monohydrate

Magnesium Stearate (E572)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store in a dry place below 25°C, protected from light.

6.5. Nature and content of container

Blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

HDPE or polypropylene containers with caps or child resistant closures in packs of 100, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for use/handling

Not applicable.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

TEVA UK Limited, Eastbourne, BN22 9AG.

Trading address:

Leeds, LS27 0JG.

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/5061R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 18 February 1982

Date of last renewal: 26 March 2002

10. DATE OF (PARTIAL) REVISION OF THE TEXT

30/01/2007

15.10 PARTICIPANT'S STUDY DIARY

PATIENT DIARY

STUDY: 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.

INVESTIGATOR: Dr K Simpson
Pain Management Services
L Ward Seacroft Hospital Leeds LS14 6UH

CONTACT DETAILS: 0113 2063132 or 0113 2063131 or 07786250784

Participant Number:

Participant's Initials:

Please complete this diary each evening before going to bed and bring it with you to your next research clinic visit on:

VISIT	DATE	TIME
2 (treatment visit)		
3 (end of study)		

Initials	Study Number	Date

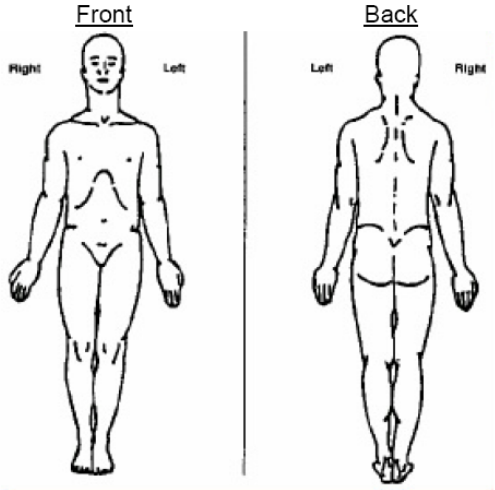
Day: -2

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

Initials	Study Number	Date

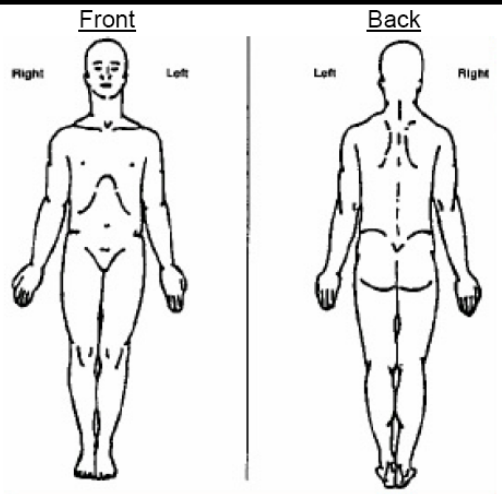
Day: -1

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

Initials	Study Number	Date

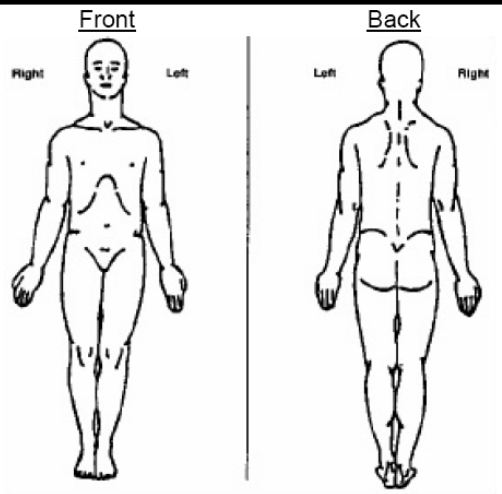
Day: 0

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

Initials	Study Number	Date

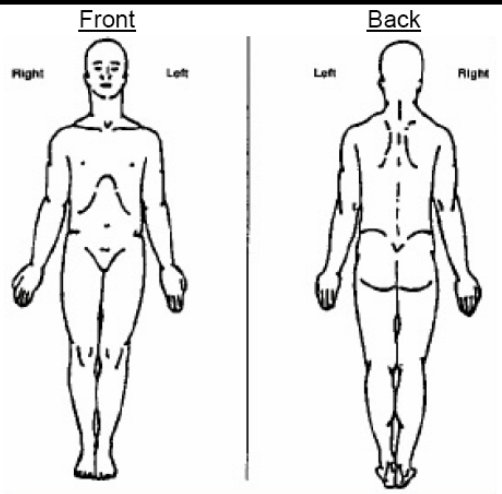
Day: 1

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

Initials	Study Number	Date

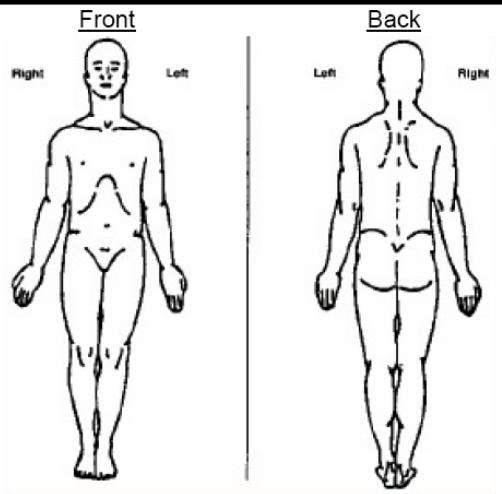
Day: 2

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

Initials	Study Number	Date

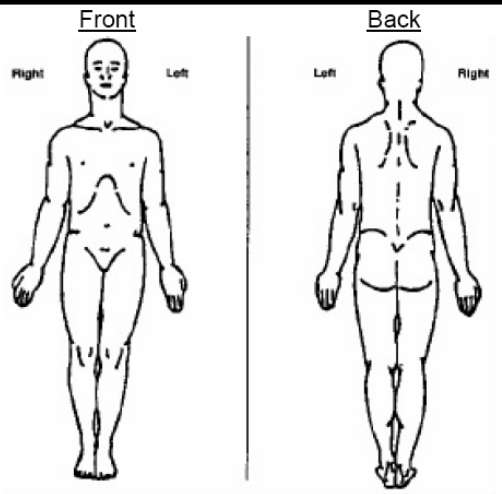
Day: 3

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

REMEMBER TO COLLECT YOUR URINE SAMPLE TOMORROW MORNING

Initials	Study Number	Date

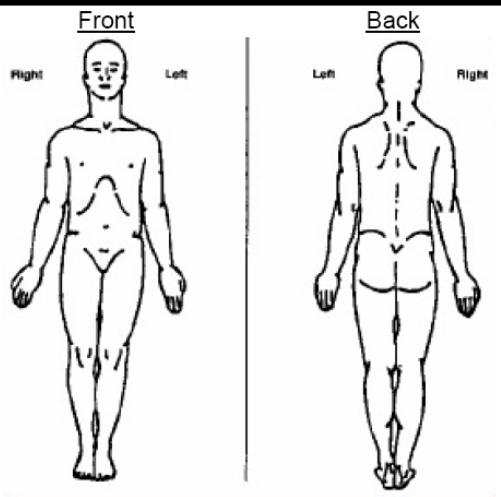
Day: 4

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

Initials	Study Number	Date

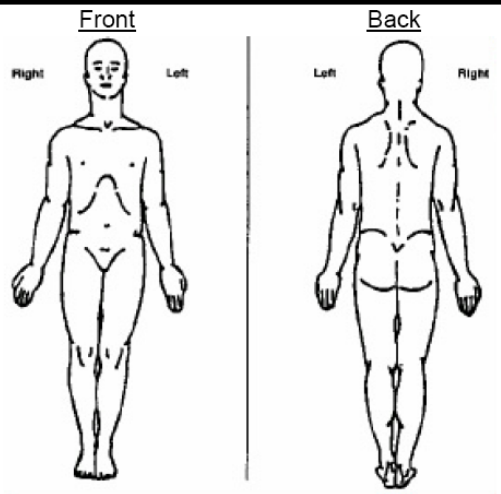
Day:

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

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☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

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8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

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9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

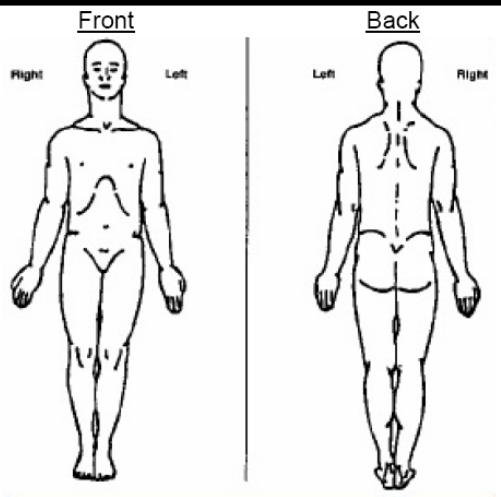
Initials	Study Number	Date

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

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4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

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A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

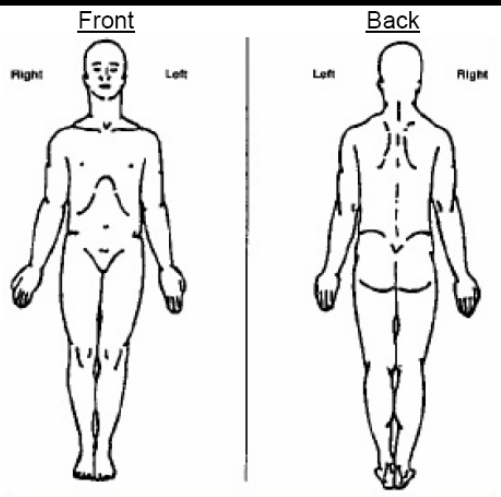
Initials	Study Number	Date

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

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No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Have you taken any extra pain killers today? YES ☐ NO ☐

If YES please complete the Medication page at the back of the diary

Have you had any new problems or side effects (for example feeling sick, constipated or headache) today? YES ☐ NO ☐

If YES please complete the Adverse Events page at the back of the diary

MEDICATION PAGE

DRUG TAKEN	**DATE**	**AMOUNT**	**TIME**	**REASON** (e.g. usual pain, new pain, headache)
E.g. Paracetamol	*3/10/08*	*1g (2 tabs)*	*3pm*	*headache*

ADVERSE EVENTS PAGE

EVENT	DATE	STARTED AT:	FINISH AT:
e.g. headache	*3/10/08*	*2.30pm*	*3.30pm*

A population study into the prevalence and genetic profile of patients with chronic pain who do not respond to oral codeine: *Oral Transudate Subset Results*

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Background

- Approximately 5-10% Caucasians are poor metabolisers (PM) of codeine and other CYP2D6 substrates because of non-functioning CYP2D6 gene alleles
- 10-15% are intermediate metabolisers (IM) who have weakened enzyme activity[1]. Normal extensive metabolisers (EM) account for 70%, however 1-3% are ultra metobolisers (UM) with multiple copies of functioning alleles, risk drug toxicity.
- The ability to predict the clinical efficacy of codeine and identify these genetic variations using an easy, repeatable, cost effective clinical test would be valuable.
- Benefits may include better patient concordance due to improved clinical response, increased safety and reduced costs. This development may be a step towards tailoring analgesic management to the individual[2].
- This study determined the proportion of chronic pain patients who lacked an analgesic response to codeine. We conducted salivary *CYP2D6* genotyping and correlated this to measurements of urine and oral transudate morphine metabolites to assess if this could predict codeine non-responsiveness in a clinical setting.

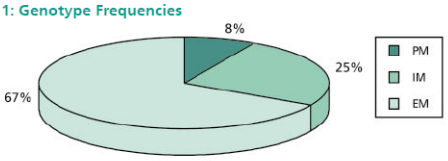
Methods

- This is an interim analysis of data being collected in a larger study. Caucasian patients attending a Pain Management clinic were recruited after informed consent (n=23, 18-80 years).
- Baseline pain assessments and concomitant medications were recorded and any prohibited analgesic medications (codeine and CYP2D6 inhibitors) were ceased. Two days later saliva was collected (Oragene•DNA Self-Collection Kit) and a baseline urine sample collected.
- Then 2 hours after oral dosing with 30mg Codeine Phosphate a sample of oral transudate was obtained via an Orasure Intercept® device for measurement of codeine and morphine metabolites.
- The patient was given a pain diary and asked to take oral codeine 30mg QDS for 5 days. On day 4 the patients collected another urine sample and returned on day 5 to provide a further urine sample, oral transudate sample and complete final pain assessments. Patients were followed up a week later to assess any adverse events.

Results

- Frequencies of genotype; PM (8.33%), IM (25%), EM (66.67%), UM (0%).
- Baseline NRS mean pain scores: 6.12 (SD 1.51, median 6, range 3-10). Day 4 mean scores: 5.83 (SD 1.81, median 5, range 2-9). 19 (79.9%) had suboptimal analgesic response to codeine (< 30% reduction in NRS).
- Urine analysis conducted in 21 patients; 3 samples excluded as missing/ leaked. Genotype PM urine samples (9.5%) were negative to morphine metabolites on day 4; IM and EM samples ranged from low to high positive for morphine metabolites (table 3).
- Five samples recorded <500 ug/L morphine (23%). 80% codeine responders had high morphine metabolites. Urine morphine metabolites were grouped and scored using a novel approach similar to a gene activity score (table 4). This showed a strong correlation (0.82) to the actual genotype.
- Oral transudate morphine metabolites did not correlate with genotype; one EM genotype produced a low positive morphine metabolite result (2.8 ug/L).

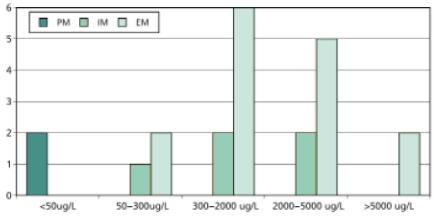
1: Genotype Frequencies



2: Analgesic Response to Codeine

NRS Score	Mean	SD	Median	Range
Baseline	6.1	1.51	6	3-10
Day 4	5.8	1.81	5	2-9

3: Morphine Metabolites in Urine



4: Urine Grouping

Urine Group Score	Morphine Metabolite Range (ug/L)
0	≤50
0.5	>50 - <300
1	>300 - 2000
2	>2000
3	>5000

Conclusion

- Prevalence of PM's was as expected from the literature.
- 10% higher proportion of *CYP2D6* IM genotypes were observed than expected.
- Genotyping is expensive and difficult to conduct in a clinical setting. Phenotyping using urine morphine metabolites is cheaper. PM status can be predicted accurately using this method.
- Low morphine metabolites (≤ 500 ug/L) indicate poor analgesic response, if no CYP2D6 inhibitors identified in concomitant medication, would clinically indicate the IM genotype.
- Oral transudate sampling was not effective in identifying CYP2D6 phenotype following codeine dosing. Larger study and further refinement of urine grouping methods is ongoing.

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15.12 Poster Abstract Presented at EFIC October 2013

Leeds Centre for Neurosciences

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CYP2D6 GENOTYPING IN A CHRONIC PAIN POPULATION: IS A FIFTH PHENOTYPE CLASSIFICATION OF 'MODERATE METABOLISER' REQUIRED FOR CONCORDANCE?

Background / Aim

- The CYP2D6 Activity Score (AS) model[1] is utilised for interpretation of phenotype from genotype.
- AS 1.0 can be allocated to Intermediate (IM) or Extensive (EM) metabolisers[2,3,4]; this contributes to potential misinterpretation in literature and clinically.
- As part of a larger study chronic pain patients were genotyped to determine the frequency of phenotypic groups to compare with reported prevalence in literature and to determine if AS 1.0 should be allocated to Moderate Metaboliser (MM).

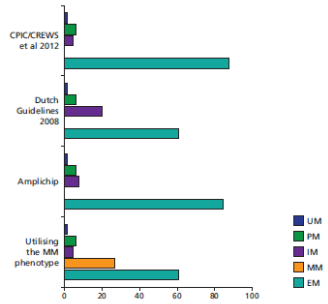
Methods

- Caucasians aged 18-80 years were recruited after informed consent (n=64).
- Salivary DNA (Oragene•DNA Self-Collection Kit) was processed by KASP™ (Kompetitive Alellen Specific PCR) for alleles *1,*2,*3,*4,*5,*6, *9, *10, *17, *41 and duplication.
- Genotypes were identified and allocated AS.
- Phenotypic status was allocated based on three separate models[2,3,4].
- Frequencies were compared for discordance.

Results

- Phenotype allocation to Poor Metabolisers (6.25%) and Ultra Metabolisers (1.5%) correlated through all models.
- IMs and EMs varied considerably depending on model from 4.7%[2] IMs to 7.8%[4] and 31.3%[3]; 61%[3] EMs compared to 84.4%[4] and 87.5%[2].

Utilising the MM phenotype



Conclusion

- Discordance in allocation of phenotypic groups according to the model used could lead to clinical error if therapy depended on knowing CYP2D6 activity.
- AS 1.0 can be classed as IM or EM, but has 50% more function than AS 0.5 (IM), and 50% less function than AS 2 (EM).
- Allocating phenotypic status MM to AS 1, representing a 50% reduction in activity compared to normal levels would provide clarity and unify this classification.

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