Clinical trial results:
A randomised, double blind, placebo controlled crossover study of the influence of the HCN channel blocker ivabradine in a healthy volunteer pain model - an enriched population study

Summary

EudraCT number	2012-005627-32
Trial protocol	GB
Global end of trial date	07 March 2016

Results information

Result version number	v1
This version publication date	02 April 2017
First version publication date	02 April 2017

Trial information

Trial identification

Sponsor protocol code	IIVoP

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust & University of Cambridge
Sponsor organisation address	Addenbrookes Hospital, Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Carrie Bayliss, CCTU Cambridge University Hospitals NHS Foundation Trust, 44 1223348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, CCTU Cambridge University Hospitals NHS Foundation Trust, 44 1223348158, cctu@addenbrookes.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2016
Global end of trial reached?	Yes
Global end of trial date	07 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

We examined whether ivabradine reduces the intensity of sensitisation induced by capsaicin. Application of capsaicin cream to the skin causes a reddening of the skin, and an increased sensitivity within the area the cream is applied (the primary hyperalgesia area) and in surrounding areas (the secondary hyperalgesia area). Changes in sensitivity can be assessed using quantitative sensory testing (QST). This will be an enriched population study, meaning that we will only include participants who respond to capsaicin. This was determined at the screening visit.

The principle research objective was to investigate whether ivabradine reduces the area of secondary punctate mechanical hyperalgesia induced by capsaicin (a change in normal sensation to a von Frey hair or pin prick stimulator).

Protection of trial subjects:

Blood pressure and heart rate monitoring was carried out during each visit and reviewed for safety before subjects were discharged from the clinical environment.

Background therapy:

Capsaicin 0.5% cream; approximately 0.5 –1ml applied topically to alternating forearms

Evidence for comparator:

The non-selective HCN channel blocking drug ivabradine is licensed for the symptomatic treatment of stable angina pectoris in patients with coronary artery disease and the treatment of heart failure. We recently investigated its effects on the symptoms of neuropathic pain in a smaller scale clinical trial (IISNeP) in 12 healthy volunteers (data not yet published). Results from this previous trial suggested that ivabradine may influence capsaicin-induced thermal and mechanical hyperalgesia, but this effect was of borderline statistical significance. However, in this initial trial there was variability in the size of the area of hyperalgesia that developed on the forearm between volunteers. The effect of ivabradine was greater in those participants who developed a large area of hyperalgesia (i.e. responded to capsaicin), providing strong justification for an enriched population trial of the influence of ivabradine on hyperalgesia in a group of capsaicin responders.
This method of recruitment for experimental clinical studies using capsaicin has been previously reported due to the occurrence of capsaicin-responders and non-responders.

Actual start date of recruitment	01 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 55
Worldwide total number of subjects	55
EEA total number of subjects	55

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects were recruited within the UK.

Pre-assignment

Screening details:

Area of capsaicin induced hyperalgesia on the screening visit was calculated to determine capsaicin-responders who proceed into the
treatment phase of the trial. A capsaicin-responder was defined as someone who has an area of punctate hyperalgesia on the forearm equal to or greater than 20 cm(2), rounded to the nearest cm(2), at at 75 minutes.

Pre-assignment period milestones

Number of subjects started	55
Number of subjects completed	27

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not fulfill screening criteria: 28

Period 1

Period 1 title	Post Screening @ 0 mins (Baseline)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Subjects, researchers & statisticians were blinded to allocation to Investigational Medicinal Product (IMP). Placebo and active medication comparator were designed and manufactured to be visually indistinguishable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivabradine First

Arm description:

Subjects were randomised to Ivabradine first and Placebo second or to Placebo first and Ivabradine second in a cross over study.

Arm type	Crossover
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg oral administration

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo containing only excipients for oral administration (indistinguishable visually from ivabradine 7.5

mg film coated tablets for oral administration).

Arm title	Placebo First
Arm description:	
Subjects were randomised to either Ivabradine first or Placebo First in a cross over design study	
Arm type	Crossover
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
7.5 mg oral administration	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
placebo containing only excipients for oral administration (indistinguishable visually from ivabradine 7.5 mg film coated tablets for oral administration).	

Number of subjects in period 1[1]	Ivabradine First	Placebo First
Started	15	12
Completed	12	12
Not completed	3	0
Early closure of study	1	-
Not contactable	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number enrolled included those subjects who were not randomised because they failed to fulfill the criteria for medical screening or were not capsaicin responders.

This is a cross over study and the numbers that enter each period are not reportable in a design that inflexibly requests inputs as though this were a parallel arm study.

Period 2

Period 2 title	Post Screening @15, 30, 45, 60 & 75 mins
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor
Blinding implementation details:	
Ivabradine and Placebo tablets were formulated to be visually identically and indistinguishable.	

Arms	
Are arms mutually exclusive?	Yes
Arm title	Ivabardine first

Arm description:

Subjects were randomised to either Ivabradine first or placebo first sequences of IMP administration

Arm type	Experimental
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg oral administration

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo containing only excipients for oral administration (indistinguishable visually from ivabradine 7.5 mg film coated tablets for oral administration).

Arm title	Placebo first

Arm description:

Subjects were randomised to receive Ivabradine or Placebo first in a double blind randomised cross-over study design

Arm type	Active comparator
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg oral administration

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

placebo containing only excipients for oral administration (indistinguishable visually from ivabradine 7.5 mg film coated tablets for oral administration).

Number of subjects in period 2	Ivabardine first	Placebo first
Started	12	12
Completed	12	12

Baseline characteristics

Reporting groups

Reporting group title	Ivabradine First

Reporting group description:

Subjects were randomised to Ivabradine first and Placebo second or to Placebo first and Ivabradine second in a cross over study.

Reporting group title	Placebo First

Reporting group description:

Subjects were randomised to either Ivabradine first or Placebo First in a cross over design study

Reporting group values	Ivabradine First	Placebo First	Total
Number of subjects	15	12	27
Age categorical			
Adults aged between 20 and 64 years old			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	15	12	27
85 years and over	0	0	0
Age continuous			
Age collected in years			
Units: years			
arithmetic mean	37.7	31.2	
standard deviation	± 13.5	± 12.5	-
Gender categorical			
Self attributed gender roles			
Units: Subjects			
Female	9	8	17
Male	6	4	10

Subject analysis sets

Subject analysis set title	Primary Endpoint - Punctate Hyperalgesia
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who passed the screening parts of the study and were randomised (regardless of contactability post randomisation).

Reporting group values	Primary Endpoint - Punctate Hyperalgesia		
Number of subjects	27		

Age categorical			
Adults aged between 20 and 64 years old			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years	27		
85 years and over			
Age continuous			
Age collected in years			
Units: years			
arithmetic mean	34.34		
standard deviation	± 12.43		
Gender categorical			
Self attributed gender roles			
Units: Subjects			
Female	17		
Male	10		

End points

End points reporting groups

Reporting group title	Ivabradine First
Reporting group description:	
Subjects were randomised to Ivabradine first and Placebo second or to Placebo first and Ivabradine second in a cross over study.	
Reporting group title	Placebo First
Reporting group description:	
Subjects were randomised to either Ivabradine first or Placebo First in a cross over design study	
Reporting group title	Ivabardine first
Reporting group description:	
Subjects were randomised to either Ivabradine first or placebo first sequences of IMP administration	
Reporting group title	Placebo first
Reporting group description:	
Subjects were randomised to receive Ivabradine or Placebo first in a double blind randomised cross-over study design	
Subject analysis set title	Primary Endpoint - Punctate Hyperalgesia
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who passed the screening parts of the study and were randomised (regardless of contactability post randomisation).	

Primary: Area of Punctate Hyperalgesia

End point title	Area of Punctate Hyperalgesia
End point description:	
Area of punctate hyperalgesia 75 minutes post application of capsaisin cream	
End point type	Primary
End point timeframe:	
Outcome at 75 minutes	

End point values	Ivabardine first	Placebo first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: cm (2)				
arithmetic mean (standard deviation)	34.898 (± 15.05)	34.05 (± 16.75)		

Statistical analyses

Statistical analysis title	Hierarchical analysis
Statistical analysis description:	
Hierarchical analysis was carried out for this endpoint to account for intra subject correlation (repeated measures) and to provide for Ivabradine versus Placebo contrasts. Restricted Maximum Likelihood was used for purposes of inferences. Where models did not converge the baseline values (invariably invariantly zero) were removed.	
Comparison groups	Placebo first v Ivabardine first

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8263
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference fixed effects
Point estimate	1.6187
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.08
upper limit	16.32
Variability estimate	Standard error of the mean
Dispersion value	7.3413

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the onset of screening to last patient last visit	
Adverse event reporting additional description:	
Information about adverse events were collected both during routinely scheduled visits as well when subjects opportunistically contacted the researchers.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	IIVoP Safety Population
Reporting group description:	
This population comprises all subjects who were exposed to any IMP	

Serious adverse events	IIVoP Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	IIVoP Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 25 (24.00%)		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Diarrhoea			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Pain in left knee		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

NONE

Notes: