



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 | v2 (current) |
| This version publication date | 17 March 2019 |
| First version publication date | 02 April 2017 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set The previous version the primary analysis wanted to model both the pre-capsaicin and post-capsaicin values. However empirically the pre-capsaicin were nearly all at the minimum value, with very little variability, which meant the model fitting was poor. A simpler model that only analyses post-capsaicin values is now used. This revised analysis corresponds to the result presented in the main study paper |

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 | 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; 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 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: To progress beyond enrollment to randomisation, patients needed to undergo an assay to determine if they satisfy the inclusion criteria. 28 patients did not, leaving 27 who were randomised.

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, Carer, Assessor |

Blinding implementation details:

Ivabradine and Placebo tablets were formulated to be visually identically and indistinguishable.

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|---|---------------------------|
| Arm title | Ivabradine |
| Arm description: | |
| Subjects were randomised to either Ivabradine first or placebo first sequences of IMP administration in a crossover design | |
| 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 | |
| Arm title | Placebo |
| Arm description: | |
| Placebo | |
| Arm type | Placebo |
| 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 | Within Patient Difference |
| Arm description: - | |
| Arm type | Crossover Comparison |
| 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 | Ivabradine | Placebo | Within Patient Difference |
|---------------------------------------|------------|---------|---------------------------|
| Started | 24 | 24 | 24 |
| Completed | 24 | 24 | 24 |

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 |

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 | Ivabradine |
| Reporting group description: Subjects were randomised to either Ivabradine first or placebo first sequences of IMP administration in a crossover design | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |
| Reporting group title | Within Patient Difference |
| Reporting group description: - | |

Primary: Area of Punctate Hyperalgesia

| | |
|---|-------------------------------|
| End point title | Area of Punctate Hyperalgesia |
| End point description: Within each patient and visit (Ivabradine or Placebo) the change from baseline to 75 minutes post application of capsaicin cream in terms of Area of punctate hyperalgesia, was calculated. Then the within-patient difference Ivabradine - Placebo was calculated. | |
| End point type | Primary |
| End point timeframe: Outcome at 75 minutes compared | |

| End point values | Ivabradine | Placebo | Within Patient Difference | |
|--------------------------------------|-----------------|-----------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 24 | 24 | |
| Units: cm (2) | | | | |
| arithmetic mean (standard deviation) | 34.9 (± 15.0) | 33.45 (± 15.3) | 1.45 (± 11.7) | |

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. | |

| | |
|---|--------------------------------|
| Comparison groups | Ivabradine v Placebo |
| Number of subjects included in analysis | 48 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.37 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.04 |
| upper limit | 10.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.5 |

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

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