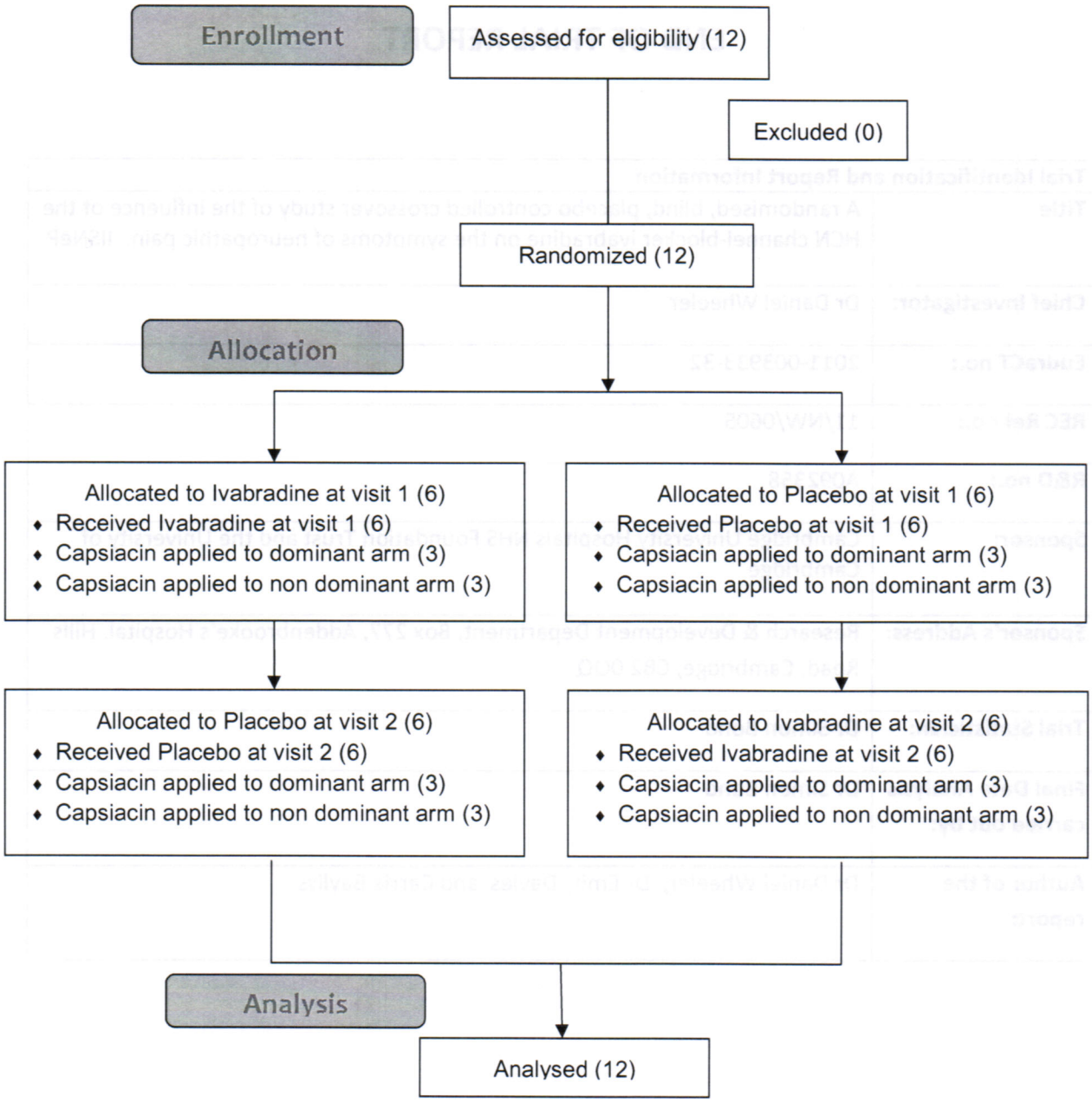
END OF TRIAL REPORT

Trial Identification and Report Information	
Title	A randomised, blind, placebo controlled crossover study of the influence of the HCN channel-blocker ivabradine on the symptoms of neuropathic pain. IISNeP
Chief Investigator:	Dr Daniel Wheeler
EudraCT no.:	2011-003933-32
REC Ref no.:	11/NW/0605
R&D no.:	A092358
Sponsor:	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Sponsor's Address:	Research & Development Department, Box 277, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ
Trial Statistician:	Dr Simon Bond
Final Data Analysis carried out by:	Dr Simon Bond
Author of the report:	Dr Daniel Wheeler, Dr Emily Davies and Carrie Bayliss


Enrollment
Assessed for eligibility (12)
Excluded (0)
Randomized (12)
Allocation
Allocated to Ivabradine at visit 1 (6)
Received Ivabradine at visit 1 (6)
Capsiacin applied to dominant arm (3)
Capsiacin applied to non dominant arm (3)
Allocated to Placebo at visit 1 (6)
Received Placebo at visit 1 (6)
Capsiacin applied to dominant arm (3)
Capsiacin applied to non dominant arm (3)
Allocated to Placebo at visit 2 (6)
Received Placebo at visit 2 (6)
Capsiacin applied to dominant arm (3)
Capsiacin applied to non dominant arm (3)
Allocated to Ivabradine at visit 2 (6)
Received Ivabradine at visit 2 (6)
Capsiacin applied to dominant arm (3)
Capsiacin applied to non dominant arm (3)
Analysis
Analysed (12)

Trial Summary	
Final Protocol version:	Version 1.0, 12 August 2011
Study Design:	A phase II, single centre, randomised, blind, placebo-controlled, 2 period cross-over trial in healthy volunteers. The purpose of the trial was to test if ivabradine, a non-selective HCN channel blocker, is an effective treatment for neuropathic pain in healthy volunteers. The key inclusion criteria were: • Aged 18 years or over • Able and willing to give written informed consent • Absence of any chronic pain medication • Volunteers in general good health The key exclusion criteria were: • Pregnancy • Pre-existing pain on either forearm • Previous surgery on either forearm • Volunteers with one arm • History of disease associated with neuropathy • Pre-existing chronic pain diagnosis or use of chronic pain medication • Hypersensitivity to capsaicin or ivabradine • Resting heart rate of less than 60 beats per minute • Systolic blood pressure of less than 90mmHg • Any recreational drug use and/or excessive alcohol consumption • Lactose intolerance (placebo may contain lactose) • Diagnosis of sick sinus syndrome • First degree atrioventricular block, or more than two ventricular extrastoles per minute • Use of CYP3A4 inhibitors such as ketoconazole, macrolide antibiotics, nefazodone, nelfinavir and ritonavir The trial was conducted over a period of 4 weeks, during which all 12 participants completed both trial visits and all assessments (excluding the cheek swab) as per protocol.
No. of participants:	12 participants were required for this trial, with all 12 being successfully recruited and treated as per protocol. Participants were randomly assigned to receive either blinded Ivabradine or placebo on visits 1 and 2 in a cross-over design. Participants were also randomised to either capsaicin application on their dominant or non-dominant arm during visit 1 in a cross over design for visit 2.
Investigational Medicinal Products:	• Ivabradine (Procorolan) 7.5mg film coated single tablet • Placebo single tablet.

	Ivabradine is licenced for use in the UK in patients with chronic stable angina pectoris in adults with coronary artery disease and is manufactured and marketed by Les Laboratoires Servier under the Marketing Authorisation EU/1/05/316/001-007 Placebo was supplied by the Royal Free Hampstead NHS Trust under the Manufacturing Authorisation MIA(IMP) 11149
Date of End of Trial:	The trial completed as per protocol on 31st January 2012
Reported Serious Breaches:	No serious breaches occurred during the trial.
Significant deviations identified during the trial:	The only protocol deviation noted during the trial was that the cheek swab for genetic analysis was not performed as per protocol. This was due to a supply problem with the cheek swab kits. As this was an exploratory secondary endpoint of the trial, failure to perform this assessment does not have any impact on the scientific validation of the trial and its primary objective.

Statistical Analysis and Main Findings	
Trial objectives and endpoints:	**Primary objective** To characterise the effect of a single dose of ivabradine versus placebo on the extent and intensity of secondary hyperalgesia induced in 12 healthy volunteers with capsaicin. **Primary endpoint** The primary endpoint is the threshold to uncomfortable heat reported by volunteers, as recorded within the area of secondary hyperalgesia elicited by capsaicin. This will be measured by contact heat evoked potential (CHEPs) quantitative sensory testing. **Secondary endpoints** The secondary endpoints are a variety of other thresholds measured by CHEPS, namely thresholds to warmth, coolness, and uncomfortable coldness. Other quantitative thresholds such as dynamic and punctate hyperalgesia will be measured. Pain intensity will be measured by means of a 100mm visual analogue scale (VAS). Genetic analysis will be conducted to examine the expression of genes encoding proteins involved in pain transmission (TRPV1) and the channels at which ivabradine act (HCN1-4). This endpoint was not measured as described in the section above.
Trial Analysis Population:	All 12 participants were successfully recruited and treated as per the originally approved protocol

Statistical Methods:	Statistical analysis was carried out as defined in the protocol and IRAS form. Efficacy endpoints were analysed using a linear mixed effects model with fixed effects for the treatment, forearm and period, adjustment for the pre-treatment heat threshold in each period, and random effects for subject. The null hypothesis was that the treatment effect would be zero. Estimates of the treatment effect (Ivabradine – Placebo) with 95% confidence intervals were provided with associated p-values. Summary statistics (mean, SD, median, max, min) were provided for the within-subject difference (ivabradine-placebo) and for each treatment based on the derived variable that is the average across repeated observation. Similar summary statistics were provided based on the change from pre- to post-treatment. A permutation test was performed on the mean within-subject differences of post- test observations. The Quantitative Sensory Test (QST) observations are the differences in means taken over repetitions at each visit. A p-value for the observed mean difference (ivabradine – placebo) was calculated and 95% confidence intervals obtained by the inverse p-value method assuming an additive treatment effect. A signed rank sum test was performed on the within-subject differences of change from pre- to post-test and a p-value produced. This tests the null hypothesis that the distribution of differences is symmetric about zero, with no further assumptions. The secondary endpoints (VAS – Visual Analogue Scale - pain assessment, area of secondary hyperalgesia) had the same analyses performed as the primary endpoint. Histograms of within-subject differences were provided for all efficacy endpoints. The number of radii used to measure the area of punctate hyperalgesia and brush allodynia was reduced to 6, and not 8 as stated in the protocol, to reduce the time taken to perform this procedure in the clinic. For statistical analysis, the formula used to calculate the area was revised accordingly. There was full compliance of all subjects, therefore the disposition table and population tables were not prepared, nor were several analyses replicated for the per-protocol population as they would be identical to the full analysis. A further post-hoc analysis was performed to calculate whether the difference in areas between ivabradine and placebo was correlated with the placebo value. The estimated slope parameters regressing the difference on the placebo value were calculated for punctate and dynamic hyperalgesia area respectively, and associated p values calculated.
Safety Information	As the trial completed and closed prior to the first anniversary, a DSUR for the trial was not submitted. However there were no SAEs, SARs or SUSARs reported during the trial period.

	The following AEs were reported during the trial period: 1 incidence of short PR interval detected on ECG 1 incidence of headache In both incidences these AEs were ongoing prior to the administration of IMP and in the case of headache, prior to the trial visit and so were considered to be unrelated and not of clinical significance to the trial.
Results:	The primary analysis is presented within the statistical report as estimate (SE). Ivabradine increased the painful heat threshold by 2.6 (1.3) degrees although this did not reach statistical significance (p=0.076). The secondary QST endpoints were all similarly non-significant. There was no evidence of an effect on the VAS score. Ivabradine showed a trend to reduce the area of hyperalgesia for both punctate and brush stimuli. A further post-hoc analysis indicated that the difference in areas between ivabradine and placebo was correlated with the placebo value. The estimated slope parameters regressing the difference on the placebo value were -0.68 (0.14) and -0.58 (0.16) for punctate and dynamic respectively with associated p values of 0.0007 and 0.0045.
Conclusion:	A possible explanation for the lack of statistical significance is that the variance parameters were underestimated and the comparisons were underpowered. The summary statistics and non-parametric tests support this conclusion. The further post hoc analysis suggests a greater effect of ivabradine in those participants that produced a large area of hyperalgesia in response to the capsaicin. Evidence from the literature suggests that participants can be grouped into responders and non-responders to capsaicin based on the mechanical hyperalgesia they display (Klein et al, 2008 Eur J Pain 12:17-29). It is possible that the study would not have been underpowered had only capsaicin responders been selected. We plan to carry out further research investigating the ivabradine effect only in participants who are defined as capsaicin responders, or investigating the regression of ivabradine effect over the continuous spectrum between non-responders and responders.

Dissemination of Research Findings and Publications	
To participants:	Participants were informed in the PIS that if they wish to obtain a copy of the results they may contact the trial doctor. No participants requested to be informed of the results of the trial and there is no plan to further disseminate the research findings to participants.
Publications:	We plan to carry out further research as stated in the conclusions section above. Results of the present study will be submitted to a peer reviewed journal either before or alongside the results of a further trial.

Chief Investigator's Signature	
	Signature: _____ Date: 13-11-2012