The role of HCN channel receptor in neuropathic pain: an open-label, single arm study of ivabradine in patients with peripheral neuropathic pain (HCN-pain)

1 Key Study Personnel

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2 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BPI	Brief Pain Inventory
cAMP	Cyclic adenosine monophosphate
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
CYP	Cytochrome P450
DAPOS	Depression, Anxiety and Positive Outlook Scale
DN4	Douleur Neuropathique 4 questionnaire
ECG	Electrocardiogram
GFR	Glomerular Filtration Rate
GP	General Practitioner
HCN	Hyperpolarization-activated cyclic nucleotide
HR	Heart Rate
GCP	Good Clinical Practice
I_h	HCN channel current
INR	International Normalised Ratio
ISI	Insomnia Severity Index
MRC	Medical Research Council
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
NPSI	Neuropathic Pain Symptoms Inventory
NRS	Numerical Rating Scale
NSAID	Non-steroidal Anti-inflammatory Drug
PDI	Pain Disability Index
PSI	Pain Severity Index
QST	Quantitative Sensory Testing
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SF-36	Short-Form Health Survey 36
SmPC	Manufacturer's Summary of Product Characteristics
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin-norepinephrine reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TUs	Treatment Units
VAS	Visual Analogue Scale

3 Study Synopsis

Title of Study	The role of HCN channel receptor in neuropathic pain (HCN pain)
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Purpose of study	To explore whether HCN receptors play a role in neuropathic pain in humans
Primary objective	To ascertain effects of HCN channel blockade on neuropathic pain.
Secondary objective (s)	To determine effects of HCN channel blockade on: [a] mechanical punctate hyperalgesia and tactile allodynia [b] self-reported sleep quality, physical disability, mood (DAPOS) and sensory qualities of neuropathic pain
Study Design	This is a single arm study designed to explore the effects of HCN receptor blockade on neuropathic pain state. Ivabradine, a nonspecific HCN blocker will be employed as the pharmacological challenge agent in this study. The drug will be administered over 6 weeks in increment doses. The dose increments are titrated to lower the heart to the target range of 50-60 beat per minutes (bpm). The maximum allowable dose is 7.5 mg twice daily
Study Endpoints	The primary endpoint is the mean of daily Pain NRS (0=no pain, 10= worst possible pain) scores calculated from recordings 7 days **before** cessation of ivabradine at Visit 5. The secondary endpoints are: • Brief Pain Inventory-SF (BPI) at visit 5 **when** ivabradine is ceased. • Insomnia Severity Index (ISI) at visit 5 **when** ivabradine is ceased. • Pain Disability Index (PDI) at the visit 5 **when** ivabradine is ceased. • Neuropathic Pain Symptom Inventory (NPSI) at the visit 5 **when** ivabradine is ceased. • Depression, Anxiety and Positive Outlook Scale (DAPOS) at the visit 5 **when** ivabradine is ceased. • Mechanical punctate hyperalgesia and tactile allodynia at the visit 5 **when** ivabradine is ceased (Section 12.2.6)
Sample Size	No more than fifty participants are to complete the treatment. Assuming a 20% study withdrawal rate, and that only a third of those screened would be eligible or available to participate, we anticipate needing to screen no more than 100 patients. Screening and enrolment will continue until interim

	analyses confirm futility (or early success)
Summary of eligibility criteria	• Be able to give voluntary written informed consent to participate • Be Male or Female and • Aged 18 years and above • Have diagnosis of peripheral neuropathy associated with pain, which includes peripheral neuropathic pain from diabetes, herpes zoster infection, or trauma to peripheral nerve trunks/ plexus (from surgery or physical injury), see Appendix 3 and DN4 score ≥ 4. • Have pain for 6 months or more • Have pain rated > 4 on a numerical rating scale (NRS) (0= No pain; 10= pain as bad as you can imagine) on at least one Pain sub-item from Brief Pain Inventory • Be registered with a GP • Have the following findings on standard ECG at screening: ▪ normal sinus rhythm (measured for 1 minute on lead II); ▪ PR interval ≤ 210 ms; ▪ QTcB ≤ 464ms for men and QTcB ≤ 474ms for women ▪ QRS duration ≤ 120 ms ▪ Heart rate ≥ 60 beats per minute
Pharmacological challenge	Oral administration of Ivabradine Ivabradine comes in the form of oral tablets. The dosage of ivabradine will range from 2.5 mg to 7.5 mg twice daily. The starting dose is 2.5mg twice daily for all participants, if tolerated, the dose will be increased every 2-3 weeks by increments of 2.5mg twice daily to a maximum of 7.5mg twice daily.
Maximum duration of treatment of a participant	The Study has a minimum of four visits, and a maximal of six visits: for **screening** (visit 1), **dose-initiation** (visits 2), **dose-adjustment** as required (visits 3 and/or 4), **dose-completion** (Visit 5), **final** (Visit 6). The baseline period between **screening** visit and **dose-initiation** has a minimum and maximum duration of 2 weeks (14 days) and 4 weeks (28 days) respectively. The interval between **dose-initiation** and 1st **dose-adjustment** visits has a minimum and maximum duration of 2 weeks (14 days) and 3 weeks (21 days) respectively. The interval between 1st and 2nd **dose-adjustment** (if required) has a minimum and maximum duration

	of 2 week (14 days) and 3 weeks (21 days) respectively. The interval between either the 1st or 2nd **dose adjustment**(s) and **dose-completion** visits has a minimum and maximum duration of 2 week (14 days) and 3 weeks (21 days) respectively. The interval between **final** and the preceding visit has a minimum and maximum duration of 2 weeks (14 days) and 3 weeks (21 days) respectively. The maximal time of participation from the point of consent is 16 weeks.
Procedures: Screening Visit 1	- Obtain written informed consent - Height in cm and Weight in Kg - Sex - Age and date of birth - Any significant past medical history/concomitant medications - Review of recreational drug/alcohol use/smoking - Urine pregnancy test (for women of child bearing potential) - Dominant or non-painful arm non-invasive blood pressure (sitting measurement) - Multi-lead ECG - Brief Pain Inventory [30] - DN4 Questionnaire - Quantitative Sensory Testing - Short Form-36 Health Survey Questionnaire SF-36 [31] - Blood sampling for serum ALT and AST, Creatinine, Haemoglobin - Issue Pain Diary
Procedures: Dose-initiation Visit 2	- AE/SAE review - Current medication review - Review pain and pulse rate diary - BPI-SF, ISI, NPSI, PDI and DAPOS - QST (see Section 12.2.6) - Rhythm strip (minimum 3 lead) ECG at rest - Dominant or non-painful arm non-invasive blood pressure (sitting measurement) - Urine pregnancy test (if applicable) - Dispensing of Study Medication
Procedure: Dose-adjustment Visit 3, 4	- AE/SAE review - Current medication review - Review pain and pulse rate diary - BPI-SF, ISI, NPSI, PDI and DAPOS - QST (see Section 12.2.6)

	- Rhythm strip (minimum 3 lead) ECG at rest - Dominant or non-painful arm non-invasive blood pressure (sitting measurement) - Urine pregnancy test (if applicable) - Ivabradine adherence review (see Section 9.1.3) - If ivabradine is being withdrawn, then sample blood for ivabradine concentrations - Dispense Study Medication (if suitable) - Tablet count
Procedure: Dose-completion Visit 5	- AE/SAE review - Current medication review - Review pain and pulse diary - BPI-SF, ISI, NPSI, PDI and DAPOS - QST (see Section 12.2.6) - Rhythm strip (minimum 3 lead) ECG at rest - Dominant or non-painful arm non-invasive blood pressure (sitting measurement) - Ivabradine adherence review (see Section 9.1.3) - Sample blood for ivabradine concentrations - Tablet count
Procedure: Final or follow-up Visit 6	- AE/SAE review - Current medication review - Review pain and pulse rate diary - BPI-SF, ISI, NPSI, PDI and DAPOS - QST (see Section 12.2.6) - Rhythm strip (minimum 3 lead) ECG at rest - Dominant or non-painful arm non-invasive blood pressure (sitting measurement)
End of Study	The participant is deemed to have finished their Study participation at the end of visit 6 (**final**).
Procedures for safety monitoring during Study	Participant will be monitored for adverse events during centre visits and telephone calls during the Study. Standard operating procedures are in place for participant safety (see Section 11)
Criteria for withdrawal of participants	Participants who fail to provide at least 50% of self-reported pain ratings per week (minimum of 3 ratings per week) in the baseline and treatment periods.

4 Study Flow Chart

5 Introduction

5.1 Background

Hyperpolarization-activated cyclic nucleotide gated (HCN) ion channels are important modulators of action potential frequency. They drive repetitive electrical activity in heart pacemaker tissue [1-3] and in some neurons [4-8] by generating an inward current, I_h, following hyperpolarization of the membrane, and so play a key role in neuronal rhythmicity.

The HCN ion channel family comprises four isoforms, HCN1-4, which carry an inward current called I_h (also I_q or I_f) [2, 3]. I_h is activated by hyperpolarization in the range of membrane potentials between -60 and -90mV, and the activation of this inward current is a major driver of the pacemaker potential in cardiac muscle [1]. The dependence of the activation of HCN2 and 4 on membrane potential is shifted in the positive direction when cyclic AMP (cAMP) binds to a domain in the C-terminal tail, a shift which increases the inward current carried by I_h in the pacemaker region of membrane potentials and thereby mediates the chronotropic action of adrenergic agonists on the heart [2, 3]. HCN1 and 3, on the other hand, are relatively insensitive to cAMP. I_h is important in driving repetitive firing in some CNS neurons [8-11] and also in primary nociceptive neurons [6, 11-15].

Previous studies have shown that HCN1 and HCN2 are the isoforms most strongly expressed in primary somatosensory neurons [13, 15-17]. Large non-nociceptive sensory neurons express a fast, cAMP-insensitive I_h attributable mainly to HCN1 [8, 15, 18, 19]. HCN1 is not functionally expressed in small neurons, the majority of which are nociceptors, apart from in a small sub-population of cold-sensitive neurons [15]. In agreement with this expression pattern, deletion of HCN1 reduces the cold allodynia seen in neuropathic pain states, but has little effect on other modalities of pain [15]. In the majority of small neurons, I_h has slower kinetics and is sensitive to intracellular cAMP, consistent with expression of HCN2 [14, 15]. Inflammatory mediators that elevate intracellular cAMP, such as prostaglandin E2 (PGE2), accelerate the frequency of action potential firing in these small neurons by an I_h-dependent mechanism [15]. These observations suggest that HCN2 may play a role in inflammatory pain, and possibly also in neuropathic pain.

5.2 Data from non-clinical studies

Recent research completed by Professor McNaughton and his team and published in Science [20] has highlighted that HCN channels play a role in controlling this hypersensitivity. Pharmacological blockade and targeted or global genetic deletion of HCN channels confirmed their role as a major modulator of the excitability of nociceptors, in particular the HCN2 channel. Pharmacological blockade and targeted or global genetic deletion of HCN channels also reduced the amount of inflammatory and neuropathic pain in experimental pain models in mice.

They bred Cre-lox knockout mice that globally lacked HCN2, and found that homozygous HCN2-/- mice showed tremor while at rest, were ataxic and underweight, and seldom lived beyond 6 weeks. In view of the adverse phenotype of global HCN2-/-, a targeted deletion was made using Cre driven by the promoter of the sodium channel isoform NaV1.8, which is expressed only in nociceptive primary sensory neurons. Thus, these mice only lack HCN2 in nociceptive neurons. They are phenotypically normal,

have similar heat thresholds and performance on the rotarod test of motor function to wild-type mice, and paw swelling in response to PGE2 injection is also similar.

Strikingly, following a sciatic nerve lesion these mice show no sign of neuropathic pain in response to thermal or mechanical stimuli. The extent of this response contrasts sharply with other pharmacological studies of HCN-mediated pain in the rat (and clinical Studys of anti-neuropathics in humans), where a 50% reduction in pain is considered highly relevant. These results show that HCN2 is a critical regulator of firing frequency in nociceptors, that neuropathic pain is initiated and maintained by HCN2-driven repetitive electrical activity in nociceptors, and moreover the importance of conducting a clinical Study of a HCN2 antagonist in neuropathic pain.

The HCN-blocker ZD7288 [21] reduces the abnormal hypersensitivity to light touch and the firing frequency of ectopic discharges in nociceptive neurons in the rat sciatic nerve ligation model [13]. ZD7288 can only be used in vitro and on experimental animals, but Ivabradine, a licensed HCN channel blocker, is available on the formulary for humans.

5.3 Human Data

5.3.1 Licensed clinical use of ivabradine

Ivabradine is the first representative of a new class of pure heart rate reducing agents – the I_f inhibitors – for the symptomatic treatment of chronic stable angina pectoris in patients in sinus rhythm who are intolerant or with a contra-indication to beta-blockers [22]. It has been extensively studied in two large, randomized controlled efficacy trials called BEAUTIFUL and SHIFT. BEAUTIFUL found that in patients taking the drug, the risk of myocardial infarction and the need for coronary revascularisation was significantly reduced [23]. SHIFT studied patients with chronic heart failure and left ventricular systolic dysfunction, and found that ivabradine reduced hospitalisation and cardiac death [24]. In 2012, Ivabradine was granted a new indication for the treatment of chronic heart failure with systolic dysfunction.

5.3.2 Safety considerations with ivabradine

For the indication of stable angina pectoris, the usual recommended starting dose of ivabradine is 5mg twice daily orally [22]. After three to four weeks of treatment, the dose may be increased to 7.5mg twice daily depending on the therapeutic response. If, during treatment, heart rate decreases persistently below 50 beats per minute at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5mg twice daily (one half 5mg tablet twice daily). Treatment must be discontinued if heart rate is consistently below 50 beats per minute, or symptoms of bradycardia persist. For chronic heart failure the same maximum dosing level of 7.5mg twice daily applies. Given limited experience in the elderly (>75 years of age) a lower starting dose of 2.5mg twice daily is recommended in both indications before titration upwards is considered if necessary.

Safety data from several clinical trials of ivabradine in patients with cardiac disease indicate that the licensed dose posology of drug is unlikely excessive in our experimental study of ivabradine in patients with neuropathic pain who are otherwise healthy.

The first ivabradine trial was a randomised, placebo-controlled, dose ranging study in 360 patients with stable angina [25]. Patients (mean age 58.5 years) were randomised

to receive placebo or one of three oral dose of ivabradine (2.5, 5, and 10mg twice daily) for 2 weeks. Ivabradine produced dose-dependent reductions versus placebo in heart rate at rest. The only adverse events linked to ivabradine treatment were visual symptoms. There was no rebound effects on HR on treatment cessation.

Subsequent data from two large RCTs for coronary heart disease indicate the drug was well-tolerated in most patients. The BEAUTIFUL Study (n=10, 907) employed a starting dose of 5mg twice daily, and did not reveal any significant increase in serious events for ivabradine compared to placebo [23]. That Study included participants aged over 55 years with a resting bpm of over 60 bpm, with a maximum dose of 7.5mg daily. The SIGNIFY Study (n=9550 on the active arm) investigated the effect of ivabradine compared with placebo on heart rate in patients with coronary artery disease [26]. The ivabradine dose regimen used in that Study (7.5 to 10 mg twice daily) was higher than the licensed posology (5 to 7.5 mg twice daily), but only included patients with a pre-treatment heart rate above 70 bpm. The results show a small but statistically significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction with ivabradine compared with placebo (7.6%, vs. 6.5% with placebo). This pertained only to a subgroup (n=6037) of participants with symptomatic angina of CCS class II or more in this subgroup.

Pre-clinical data from McNaughton lab has revealed a strong dose response relationship for the analgesia effects of ivabradine [27]. Importantly, the IC50 for heart rate (HR) and analgesic effects are similar, with maximal analgesia occurring when the effect of ivabradine on heart rate plateaus. These data suggest that the efficacy of ivabradine on neuropathic pain in patients, if present, are best revealed at higher concentrations of the drug. Whilst patients with peripheral neuropathic pain who are otherwise healthy are likely to be at lower risk for cardiac events, that risk remains to be ascertained. Hence, employing a fixed maximum dose in this group of patients, would be difficult to justify, and may lead to participant withdrawal from adverse events. These considerations have led to the approach taken in this open-label studies, which is to employ gradual dose titration to maximal tolerated HR (based on ECG monitoring, and subjective symptoms) in individuals. This optimises detection of a significant analgesic drug effect whilst ensuring the participants' safety.

Contraindications to ivabradine include, but are not limited to; sick sinus syndrome, sino-aStudy block and concomitant use with cytochrome P450(CYP) 3A4 inhibitors such as ketoconazole, itraconazole macrolide antibiotics, nefazodone and the anti-retrovirals nelfinavir and ritonavir. For a complete list of contraindications please refer to the Summary of Product Characteristics (SmPC) for ivabradine, referenced in section 9.3.

Almost 15% of individuals taking ivabradine experience luminous visual phenomena due to blockage of I_h ion currents in the retina. These symptoms are mild, transient, fully reversible and non-severe. In clinical trials less than 1% of all patients had to discontinue the drug because of these sensations, which occurred within the first two months after commencement of the drug [28]. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. The incidence of bradycardia is 3.3% particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm. Other reported adverse drug reactions that occur in 1-10% of patients include first degree atrioventricular block, ventricular extra systoles, dizziness, headache, uncontrolled blood pressure and blurred vision [22].

5.3.3 Pharmacokinetics & pharmacodynamics of ivabradine

The established pharmacodynamic property of ivabradine in humans is a specific dose-dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20mg twice daily indicates a trend towards a plateau effect, which is consistent with a reduced risk of severe bradycardia. At 20mg of ivabradine daily, a 17-20% heart rate reduction occurs at rest [25, 29]. This slowing of the heart rate appears to be the means by which ivabradine exerts its beneficial effects: a reduction in myocardial oxygen demand reduces myocardial ischaemia, and hence angina and infarction.

Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting conditions. The absolute bioavailability of the film-coated tablets is around 40% due to first-pass effect in the gut and liver. Food delays absorption by approximately 1 hour and increases plasma exposure by 20-30%, which reduces intra-subject variability, hence participants would be advised to take the tablets with meals in this study. Its main plasma half-life is 2 hours.

Furthermore, passage of ivabradine into the brain (as assessed using total radioactivity) is very low; its activity is therefore considered to be strictly peripheral.

6 Rationale for Study

Our hypothesis is that HCN-2 receptors maintain neuropathic pain in humans, and if so, blockade of HCN-2 receptors would result in a reduction of neuropathic pain. HCN-2 specific antagonists are currently unavailable for use in humans. Hence, we employ ivabradine, a non-specific but peripherally restricted HCN antagonist, for our purpose. Ivabradine does not cross the blood-brain barrier, hence, it is likely to be efficacious for neuropathic pain of peripheral origin. Consequently, we plan to study the HCN system in patients with peripheral neuropathic pain only. Their diagnoses would include diabetic neuropathy, post-herpetic neuralgia, and iatrogenic (post-surgical or post-traumatic) neuralgias affecting the limb.

This study is important because neuropathic pain is difficult to treat and places a great burden on individuals who suffer from it, their families and carers, and society as a whole. There has not been a new anti-neuropathic drug for more than 5 years. The present research would assess whether the HCN receptor system plays a role in human pain, given the strong evidence for its role in animal models. Evidence of a role for the HCN system in humans for pain, would suggest that drug modulation of this system would benefit neuropathic pain, and provide the go-ahead for rapid development of more specific HCN agonists and testing in formal clinical efficacy trials

The healthcare benefits of new drugs for neuropathic pain are considerable. Pain relief would improve the quality of life and physical function in patients who are currently crippled by the condition. Additionally, animal data now reveal that HCN blockers may also be efficacious for pain from acute or chronic inflammation. This study represents the first step in establishing the proof of principle for the role of HCN blockers in managing a broad range of chronic pain syndromes.

7 Study Design

7.1 Statement of design

This is a single arm study designed to explore the effects of HCN receptor blockade on neuropathic pain state. Ivabradine, a nonspecific HCN blocker will be employed as the pharmacological challenge agent in this study. The drug will be administered over 6 weeks in increment doses. The dose increments are titrated to lower the heart to the target range of 50-60 beat per minutes (bpm). The maximum allowable dose is 7.5 mg twice daily.

7.2 Participant Invitation

This is a single-centre study being conducted at the Addenbrookes Centre of Clinical Investigation, a purpose built facility for experimental medicine studies within Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge.

Potential participants would be identified by

- Database search and invitation by the relevant Clinical Specialists in the NHS Hospital Trusts
- Database search and invitation through Primary Care (GP) Practices
- Public advertisement by word-of-mouth, websites, paper and electronic posters on designated university and hospital sites, and newspapers.

Potential participants can register their interest and contact the research team by post (using a self-addressed reply slip), email or telephone. They would then be sent a Participant Information Sheet (PIS), and be invited to make further contact with the research team. The research team can contact the potential participant once to follow-up on interest for up to 3 weeks after sending the participant information sheet. The research team will clarify details and instructions contained in the PIS if required. A screening visit would be arranged for those who remain interested.

7.3 Number of Subjects

No more than fifty participants are to complete the treatment. Assuming a 20% study withdrawal rate, and that only a third of those screened would be eligible or available to participate, we anticipate needing to screen no more than 100 patients. Screening and enrolment will continue until interim analyses confirm futility (or early success), or when 50 participants complete the dose cessation and follow-up visits.

7.4 Study duration

The active participation duration for each patient will be approximately 10 weeks, not including time to consider his or her participation in the Study. This will include 6 visits to Addenbrooke's hospital (1 screening visit, 1 dose-initiation visit, 2 dose-adjustment visits, 1 dose-completion visit and 1 follow-up visit) and up to 2 pre-arranged telephone calls between visits to encourage adherence to Study procedures and schedule visits. Further telephone communications may become necessary, in which case, the investigator/study team will document the purpose and outcome of each call.

An overview of the patient study schedule is presented below.

VISIT ONE	Check HR	Action	Proceed to
Screening	<60bpm	Exclude participant	
	≥ 60bpm	Include Participant	Visit 2
	Interval (days) 14-28		

VISIT TWO	Check HR	Action	Prescribe	Proceed to
Dose initiation	< 60bpm	Withdraw participant	-	
	≥ 60bpm	Start dose	2.5mg twice daily for 21 days	Visit 3
	Interval (days) 14-21			

VISIT THREE	Check HR	Action	Prescribe	Proceed to
Dose adjustment	>60bpm	Increase dose: by 2.5 mg twice daily	5mg twice daily for 21 days	Visit 4
	≥50-60bpm	Maintain dose at 2.5mg twice daily	2.5 mg twice daily for 21 days	Visit 4
	<50bpm	Cease dosing		Visit -6
	Interval (days) 14-21			

VISIT FOUR	Check dose	Check HR	Action	Prescribe	Proceed to
Dose adjustment	2.5mg twice daily	>= 50 bpm	Maintain dose	2.5 mg twice daily for 21 days	Visit 5
		< 50 bpm	Cease dose		Visit 6
	5mg twice daily	>60 bpm	Increase dose by 2.5mg	7.5mg twice daily for 21 days	Visit 5
		51-60 bpm	Maintain dose	5mg twice daily for 21 days	Visit 5
		<50 bpm	Decrease dose by 2.5mg	2.5mg twice daily for 21 days	Visit6
	Interval (days) 14-21				

VISIT FIVE Dose cessation	Action	Proceed to
	Stop dose	Visit 6
	Interval (days) 14-21	
VISIT SIX Final	**Action**	
	Follow-up	

7.5 Study objectives

7.5.1 Primary objective

To ascertain effects of HCN channel blockade on neuropathic pain.

7.5.2 Secondary objectives

To determine effects of HCN channel blockade on:

[a] mechanical punctate hyperalgesia and tactile allodynia
[b] self-reported sleep quality, physical disability, mood (DAPOS) and sensory qualities of neuropathic pain

7.6 Study endpoints

7.6.1 Primary endpoint

The primary endpoint is the mean of daily Pain NRS (0=no pain, 10= worst possible pain) scores calculated from recordings 7 days **before** cessation of ivabradine at Visit 5.

7.6.2 Secondary endpoints

The secondary endpoints are:

- Brief Pain Inventory-SF (BPI) at visit 5 **when** ivabradine is ceased.
- Insomnia Severity Index (ISI) at visit 5 **when** ivabradine is ceased.
- Pain Disability Index (PDI) at the visit 5 **when** ivabradine is ceased.
- Neuropathic Pain Symptom Inventory (NPSI) at the visit 5 **when** ivabradine is ceased.
- Depression, Anxiety and Positive Outlook Scale (DAPOS) at the visit 5 **when** ivabradine is ceased.
- Mechanical punctate hyperalgesia and tactile allodynia at the visit 5 **when** ivabradine is ceased (Section 12.2.6)

7.6.3 Exploratory endpoints

Exploratory endpoints may include using

- baseline psychometric differences (DN4 and SF-36 questionnaires) and plasma concentrations of ivabradine to explain variation in the magnitude of change in pain scores and HR related to HCN agonism in individuals.

8 Selection and withdrawal of participants

8.1 Inclusion Criteria

To be included in the Study the subject must:

- Be able to give voluntary written informed consent to participate
- Be Male or Female and
- Aged 18 years and above
- Have diagnosis of peripheral neuropathy associated with pain, which includes peripheral neuropathic pain from diabetes, herpes zoster infection, or trauma to peripheral nerve trunks/ plexus (from surgery or physical injury), see Appendix 3 and DN4 score ≥ 4.
- Have pain for 6 months or more
- Have pain rated > 4 on a numerical rating scale (NRS) (0= No pain; 10= pain as bad as you can imagine) on at least one Pain sub-item from Brief Pain Inventory

- Be registered with a GP
- Have the following findings on standard ECG at screening:
  - normal sinus rhythm (measured for 1 minute on lead II);
  - PR interval ≤ 210 ms;
  - QTcB ≤ 464ms for men and QTcB ≤ 474ms for women
  - QRS duration ≤ 120 ms
  - Heart rate ≥ 60 beats per minute

8.2 Exclusion Criteria

The subject who meets any of the following criteria will be excluded from participating in the Study:

- Known to be allergic to ivabradine or have hypersensitivity to any of the formulation ingredients
- Current treatment with ivabradine
- Use of drugs with potential serious interactions with Ivabradine – as indicated by the latest version of British National Formulary at the time of screening
- Is currently receiving or have received prior to the screening (Visit 1) any of Prohibited Concomitant Medications (see section 21.3.1).
- Have Pain Severity Index greater than 9 on the Brief Pain Inventory Short-Form (BPI-SF)
- Is scheduled for clinical treatment (e.g. drugs, psychological therapy, surgical or interventional treatment) for any chronic pain or other health condition for the anticipated duration of the Study
- New York Heart Association heart failure class II or higher, or hospitalization for heart failure within a year
- Myocardial infarct, coronary revascularization, stroke or transient ischemic attack within 6 months of the screening visit
- Transplanted heart, implanted pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy
- Is scheduled for coronary revascularization; or likely to require cardiac surgery for valvular disease
- Known congenital long QT, permanent atrial fibrillation or flutter, sick sinus syndrome, sinoatrial block, second and complete atrio-ventricular block
- Severe or uncontrolled hypertension with systolic BP > 180mmHg or diastolic BP > 110 mmHg after sitting for at least 5 minutes
- Sitting systolic BP < 85mmHg or symptomatic hypotension
- Active uncontrolled psychiatric illness (e.g. severe depression (risk of self-harm), schizophrenia, substance misuse or dependence)
- Known severe renal disease, or moderate or severe liver disease
- Known to be HIV, Hepatitis B or C seropositive (Level 3 containment laboratory procedures are not available for the handling of infectious specimens)
- Any illness or condition that in the opinion of the PI or delegated investigators, precludes safe participation in the Study or interferes with Study procedures.
- Currently participating in any interventional Study, have participated in an interventional Study within 12 weeks of screening or are currently enrolled in a non-interventional Study, which participating in this Study would impact upon
- Unwilling for the GP to be notified or to provide information relevant to the participation of the clinical Study
- Transaminases ALT and AST greater than three times the upper normal limit
- Haemoglobin <11.0g/dL
- Creatinine clearance (Cockcroft-Gault – section 21.4) < 50 ml/min/1.73m^2
- Females of childbearing potential, or males who decline to use adequate contraceptive measures for the duration of the Study as listed in section 10.6

- Is pregnant or breast feeding
- Reports consuming more than 28 units of alcohol per week for a man, or 21 units of alcohol per week for a woman
- Reports current recreational drug use
- Who, in the opinion of the PI and delegated investigators, are unable or unlikely to comply with the Study requirements or procedures

8.3 Subject withdrawal criteria

Participants can withdraw from the study at any time, either voluntarily (consent withdrawal) or upon the decision of the investigator (premature withdrawal).

8.3.1 Planned subject withdrawal criteria

The planned withdrawal criteria are as follows:

- Participants who fail to provide at least 50% of self-reported pain ratings per week (minimum of 3 ratings per week) in the baseline and treatment periods.

8.3.2 Others

The researcher will also withdraw any Participant if he/she believes the safety of the participant is compromised. This includes, but is not limited to, major deviation to the protocol incompatible with continuation of treatment (e.g. pregnancy), in the event of a treatment-related serious adverse event (SAR) or suspected unexpected serious adverse reaction (SUSAR).

All reason(s) for withdrawal will be documented by the researcher in the participant's case report form.

9 Pharmacological challenge (ivabradine administration)

9.1 Dosage schedules

9.1.1 Route of Administration and Maximum dosage allowed

Ivabradine comes in the form of oral tablets. The dosage of ivabradine will range from 2.5 mg to 7.5 mg twice daily. The starting dose is 2.5mg twice daily for all participants, if tolerated, the dose will be increased every 2-3 weeks by increments of 2.5mg twice daily to a maximum of 7.5mg twice daily.

All participants would be advised to consume ivabradine with food.

9.1.2 Maximum duration of ivabradine administration treatment of a participant

Three weeks' supply of ivabradine would be prescribed if the participant is suitable after each review of daily pulse rates and visit ECG. The daily pulse rates will be measured by the participant after they have been trained in the procedure. The ECG review occurs within 14 days to 21 days after each new prescription of ivabradine. Hence, the maximum duration of ivabradine treatment is 9 weeks.

9.1.3 Procedures for monitoring subject compliance

Any unused tablets would be collected and counted, and extra, or missing tablets would be recorded at dose adjustment or dose cessation visits. Participants would also be asked whether they have taken about the same, more or less of their usual medications for pain, and the reason why would be recorded, during these visits.

Adherence to ivabradine would be encouraged at each visit and telephone appointments. Blood would be sampled for plasma ivabradine and active metabolites just before drug is ceased by the researcher. Note that the drug can be ceased at dose adjustment or dose cessations visits. The sample would be analysed collectively after the end of the Study (Section 14.5).

These data may be employed to explain the inter-individual variation in primary outcome measure.

9.2 Presentation of the drug

9.2.1 Ivabradine

Ivabradine is currently available as 5mg and 7.5mg tablets. The 5mg tablets are scored to enable 2.5mg dosing. Any UK-licensed brand of ivabradine is acceptable for use in the study.

9.3 Known drug reactions & interaction with other therapies

Please see the latest SmPC for ivabradine. The most common known reactions of this drug are luminous visual phenomena (transient enhanced brightness in a limited area of the vision), blurred vision, headache, bradycardia (low heart rate which can result in dizziness and fainting), first-degree atrioventricular block and ventricular extrasystole. Less-common adverse reactions include eosinophilia, hyperuricaemia, dyspnoea (breathlessness), asthenia, fatigue, malaise, elevated creatinine in blood, ECG prolonged QT interval, angiodema, nausea, constipation, diarrhoea, palpitations, vertigo and muscle cramps, itching (pruritus), skin rash, skin reddening (erythema) and syncope.

9.4 Dosage modifications

The dosage will be modified according to HR at the start of the dose-adjustment visits. Please refer to the tables (study schedule) in Section 7.4 for details.

9.5 Legal status of the drug

Ivabradine is currently manufactured and marketed by Servier and licensed for use in the UK in adults with chronic stable angina pectoris with coronary artery disease and in patients for treatment of chronic heart failure.

Ivabradine will only be prescribed by suitably qualified researchers, for the participants specified in this protocol, and within the study.

9.6 Drug storage and supply

The Pharmacy department will be responsible for receipt, storage and dispensing according to the study design.

Ivabradine should be stored in a secure area with restricted access, in dry conditions, at room temperature (up to 30°C).

10 Procedures and assessments

All Participants will attend a screening visit in which assessment of their eligibility for the study would commence.

10.1 Screening evaluation

All patients will be allocated a Study-specific unique identifier (Study ID) at the point of entry into the Study (when they sign Informed Consent).

All participants will have a full medical history taken and a clinical examination. The following data points are to be recorded:

- Obtain written informed consent
- Height in cm and Weight in Kg
- Sex
- Age and date of birth
- Any significant past medical history/concomitant medications
- Review of recreational drug/alcohol use/smoking
- Urine pregnancy test (for women of child bearing potential)
- Dominant or non-painful arm non-invasive blood pressure (sitting measurement)
- Multi-lead ECG
- Brief Pain Inventory [30]
- DN4 Questionnaire
- Quantitative Sensory Testing
- Short Form-36 Health Survey Questionnaire SF-36 [31]
- Blood sampling for serum ALT and AST, Creatinine, Haemoglobin
- Issue Pain Diary

The duration of Visit 1 is about 2 hours. After Visit 1, laboratory results would be traced to confirm the eligibility of the participant for the subsequent Study Visits. The participant is only eligible for the treatment phase of the Study if he/she fulfils all Inclusion/Exclusion criteria.

The participant would be notified by Telephone of the outcome of the screening visit. Abnormal results from laboratory-based tests would be sent to the General Practitioner with consent from the potential participant. The General Practitioner may also be contacted to verify current prescriptions and medical history relevant to screening for eligibility.

If the patient is deemed eligible, he/she will proceed to the treatment assessments listed below. Appointments for further study visits (dose initiation, dose adjustment, dose cessation and final) would be arranged during their visits or by Telephone or Email.

10.2 Study assessments

10.2.1 Timing of Study Visits

The Study has a minimum of four visits, and a maximal of six visits: for **screening** (visit 1), **dose-initiation** (visits 2), **dose-adjustment** as required (visits 3 and/or 4), **dose-completion** (Visit 5), **final** (Visit 6).

The baseline period between **screening** visit and **dose-initiation** has a minimum and maximum duration of 2 weeks (14 days) and 4 weeks (28 days) respectively.

The interval between **dose-initiation** and 1st **dose-adjustment** visits has a minimum and maximum duration of 2 weeks (14 days) and 3 weeks (21 days) respectively.

The interval between 1st and 2nd **dose-adjustment** (if required) has a minimum and maximum duration of 2 week (14 days) and 3 weeks (21 days) respectively.

The interval between either the 1st or 2nd **dose adjustment**(s) and **dose-completion** visits has a minimum and maximum duration of 2 week (14 days) and 3 weeks (21 days) respectively.

The interval between **final** and the preceding visit has a minimum and maximum duration of 2 weeks (14 days) and 3 weeks (21 days) respectively.

The maximal time of participation from the point of consent is 16 weeks.

10.2.2 Assessment data at Visit 2 (**dose-initiation**)

The following are to be recorded at Visit 2. The duration of Visit 2 is about 1.5 hours. Visit 2 occurs between 14 to 21 days after the screening visit.

- AE/SAE review
- Current medication review
- Review pain and pulse rate diary
- BPI-SF, ISI, NPSI, PDI and DAPOS
- QST (see Section 12.2.6)
- Rhythm strip (minimum 3 lead) ECG at rest
- Dominant or non-painful arm non-invasive blood pressure (sitting measurement)
- Urine pregnancy test (if applicable)
- Dispensing of Study Medication

10.2.3 Assessment data at Visit 3 and 4 (**dose-adjustment**)

The appointment (date and time) for Visit 3 and 4 would be made prior to each visit, either at the preceding Visit or via telephone/email after the preceding visit. The dose-adjustment visit occurs between 14 to 21 days after the preceding visit. Each visit is about 1.5 hours. The following are to be recorded at these Visits:

- AE/SAE review
- Current medication review
- Review pain and pulse rate diary
- BPI-SF, ISI, NPSI, PDI and DAPOS
- QST (see Section 12.2.6)
- Rhythm strip (minimum 3 lead) ECG at rest
- Dominant or non-painful arm non-invasive blood pressure (sitting measurement)
- Urine pregnancy test (if applicable)
- Ivabradine adherence review (see Section 9.1.3)
- If ivabradine is being withdrawn, then sample blood for ivabradine concentrations
- Dispense Study Medication (if suitable)
- Tablet count

10.2.4 Assessment data at Visit 5 (**dose-completion**)

The duration of Visit 5 is about 1.5 hours. The appointment (date and time) is made at Visit 4 or via telephone or email after the preceding visit. Visit 5 occurs between 14 to 21 days after the preceding visit. The following are to be recorded:

- AE/SAE review
- Current medication review
- Review pain and pulse diary
- BPI-SF, ISI, NPSI, PDI and DAPOS
- QST (see Section 12.2.6)
- Rhythm strip (minimum 3 lead) ECG at rest
- Dominant or non-painful arm non-invasive blood pressure (sitting measurement)
- Ivabradine adherence review (see Section 9.1.3)
- Sample blood for ivabradine concentrations
- Tablet count

10.2.5 Assessment data at visit 6 (**final**)

Visit 6 is the last Study Visit. The duration of Visit 6 is 1.5 hours. The appointment (date and time) for Visit 6 is made at the preceding visit or via telephone or email after the preceding visit. Visit 6 occurs between 14-21 days after cessation of Study medication. The following are to be recorded at Visit 6:

- AE/SAE review
- Current medication review
- Review pain and pulse rate diary
- BPI-SF, ISI, NPSI, PDI and DAPOS
- QST (see Section 12.2.6)
- Rhythm strip (minimum 3 lead) ECG at rest
- Dominant or non-painful arm non-invasive blood pressure (sitting measurement)

10.3 Long-Term Follow-up Assessments

There are no long-term follow-up assessments.

10.4 End of Study Participation

The participant is deemed to have finished their Study participation at the end of visit 6 (**final**).

10.5 Schedule of Assessments

Visits and Procedures	Screening	Initiation	Adjustment		Cessation	Follow-up
	1	2	3	4	5	6
Inclusion/Exclusion criteria	X					
Informed consent	X					
Medical History	X					
Current Medication use	X	X	X	X	X	X
Height and weight measurements	X					
AE/SAE review		X	X	X	X	X
History of illicit drug use. smoking and alcohol consumption	X					
Urine pregnancy test (as necessary)	X	X	X	X		
Multi-lead ECG (usually 12 lead)	X					
Blood pressure measurements	X	X	X	X	X	X
ECG (rhythm strip – 3 lead minimum)		X	X	X	X	X
Issue pain and pulse rate diary	X	X	X	X	X	
Review pain and pulse rate diary		X	X	X	X	X
DN4, SF-36	X					
BPI-SF	X	X	X	X	X	X
ISI, NPSI, PDI, DAPOS		X	X	X	X	X
Quantitative Sensory Testing (QST)	X	X	X	X	X	X
Dispense Study Medication		X	X	X		
Ivabradine adherence review			X	X	X	
Obtain blood sample once after withdrawal of Study medication only	X		X	X	X	
Total Time for visit (hours)	2	1.5	1.5	1.5	1.5	1.5

10.6 Study restrictions

Participants should not consume grapefruit or grapefruit juice whilst participating in this Study as grapefruit can increase systemic exposure to ivabradine.

Participants should keep prescribed analgesic and other medication use stable during the Study.

One of the potential side effects of ivabradine is luminous visual phenomena. If the participant experiences this side effect they must refrain from driving until it has passed.

Women on the study must avoid becoming pregnant by taking adequate precautions with birth control for at least one month before the screening visit until 7 days after the last dose of ivabradine. These precautions include:

- Intrauterine device (IUD)
- Hormonal-based contraception (pill, contraceptive injection, etc.)
- Double barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicides

- True abstinence where it is in line with the participant's preferred and usual lifestyle (no sexual activity from 1 day before the 1st dose until 7 days after the last dose of ivabradine).

Females who are post-menopausal (at least 1 year prior to the screening visit), sterile or have undergone sterilisation do not require contraception for the study.

Men must agree to use the following reliable forms of contraception after the first drug dose until 7 days after the last dose of ivabradine:

- A condom and spermicide even if female partner(s) is using another method of contraception. (Men should also use a condom to protect female partners from exposure to the study medicine in semen.)
- True abstinence where it is in line with the participant's preferred and usual lifestyle (no sexual activity with female partner(s) after the first drug dose until the last Study visit). If men become sexually active they must use the method listed above.

11 Assessment of Safety

11.1 Definitions

11.1.1 Adverse event

Any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with ivabradine.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of ivabradine, whether or not considered related to ivabradine.

11.1.2 Adverse reaction to ivabradine (AR)

All untoward and unintended responses to ivabradine related to any dose administered. All adverse events judged by either the reporting researcher or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the summary of product characteristics (SmPC) for ivabradine. When the outcome of the adverse reaction is not consistent with the SmPC, this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on participant/event outcome or action criteria.

11.1.4 Serious adverse event or serious adverse reaction

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
- results in persistent or significant disability or incapacity,

- is a congenital anomaly or birth defect.
- Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical events should be reported on the serious adverse event (SAE) form under the 'other' category.

11.2 Expected Serious Adverse Drug Reactions

The adverse reactions expected from taking Ivabradine are listed in section 9.3. The adverse reaction should be escalated to a Serious Adverse Reaction if the defining criteria in section 11.1.4 are met and should be recorded on appropriate CRFs and reported to the Sponsor as per section 11.7.

11.3 Expected Serious Adverse Events

No serious adverse events are expected in this study.

11.4 Expected Adverse Reactions

The known side effects of ivabradine are described in section 4.8 of the SmPC, Undesirable Effects. They are generally not serious in nature and will only be recorded in the AE/AR Log as part of this Study.

11.5 Expected Adverse Events

The following adverse events are known side effects of blood sampling; bruising and discomfort around the site where the blood has been drawn.

These expected AEs are generally not serious in nature and will <u>not</u> be recorded in the AE/AR Log as part of this Study.

11.6 Recording and evaluation of adverse events

The researcher should evaluate each adverse event. This includes the evaluation of its seriousness, causality and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event. Please see Appendix 2 for further information.

11.6.1 <u>Assessment of seriousness</u>

Seriousness is assessed against the criteria in section 11.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction.

11.6.2 <u>Assessment of causality</u>

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a

plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

11.6.3 Clinical assessment of severity

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the subject's life is at risk from the event.

11.7 Reporting serious adverse reactions

The Chief Investigator would assessing all ARs and SARs for expectedness and notification of all SARs to the Sponsor immediately but not more than 24 hours of first awareness. The sponsor has to keep detailed records of all SARs reported to them by the Study team.

An adverse event or reaction that meets serious criteria irrespective of consistency (expected or unexpected) of ivabradine (summary of product characteristics) must be reported to the sponsor.

11.8 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All unexpected and serious (SUSARs) are subject to expedited reporting.

11.8.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification to the REC to the Chief Investigator. The Chief Investigator should report on the AE/SAE form all the relevant safety information previously described, to the Sponsor, any concerned competent authorities, and to the Ethics Committee concerned.

11.8.2 When to report?

11.8.2.1 Fatal or life-threatening SUSARs

The Research Ethics Committee and Sponsor should be notified as soon as possible but no later than **7 calendar days** after the Study team and Sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the Ethics Committee and Sponsor within an additional **8 calendar days**.

11.8.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to the Sponsor and Ethics Committee as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up

information should be given as soon as possible.

11.8.3 How to report?

11.8.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. Initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) the suspected drug (ivabradine),
b) an identifiable subject (e.g. Study ID),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source, and, when available and applicable: e.g. a unique study identification (e.g. REC/ Sponsor's code numbers)

11.8.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

11.9 Pregnancy Reporting

All pregnancies within the Study (either the Study participant or the participant's partner) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

12 Evaluation of Results (Definitions and response/evaluation of endpoints)

12.1 Primary Endpoint

The primary efficacy endpoint is the mean pain score.

The mean pain scores are derived from daily pain ratings recorded by the participant using an 11-point numerical rating score ranging from 0 to 10. The participant would evaluate the pain **at least once daily**, starting from after **Screening** visit until **Final** visit.

For each evaluation of pain, the participant would record the number on the NRS scale that best described his or her pain. Participants would be instructed and reminded to focus on and rate pain whose qualities are neuropathic in nature (as described by the adjectives in the DN4 questionnaire).

The baseline period is the period before and leading to Dose-Initiation visit. The **baseline mean** pain score is calculated as the mean of all the entries before the participant takes the first dose of ivabradine. NRS scores do not need to be available for

consecutive days. The minimum number of entries required is 1 per day for 7 days (see Section 8.3.1).

The treatment period is defined as the 14 days leading up to the last dose of ivabradine. For the treatment period, the **endpoint mean** score is calculated as the mean of all the diary entries made in the 10 days leading up to the visit when the treatment is discontinued. The entries made in the first 4 days after dose initiation or adjustment are ignored for this analyses because ivabradine plasma levels takes time to reach plateau. NRS scores do not need to be available for consecutive days. The minimum number of entries required (after discarding the first 4 entries) is 1 per day for 7 days. Please also refer to Section 8.3.1 Planned Subject Withdrawal Criteria.

The change-from-baseline is calculated as the **endpoint mean** score minus the **baseline mean** score.

12.2 Secondary Endpoints

12.2.1 Brief Pain Inventory-SF (BPI-SF)

Items 3 to 6 assess pain at its 'least', 'worst', 'average', and 'right now' on a 11 point NRS. The average score from four items comprise the Pain Severity Index [32].

12.2.2 Insomnia Severity Index (ISI)

The ISI consists of 7 items that assesses sleep quality [33]. Each item is scored on a 5 point Likert Scale (0-4). The ISI is the sum of scores from all 7 items.

12.2.3 Neuropathic Pain Symptom Inventory (NPSI)

The NPSI allows discrimination and quantification of the distinct and clinically relevant dimensions of neuropathic pain syndromes (spontaneous ongoing pain, spontaneous paroxysmal pain, evoked pain, and paresthesia/dysesthesia) that may be relevant to treatment [34, 35]. The NPSI includes 12 items; 10 are descriptors of the different symptoms, and 2 assess the duration of spontaneous ongoing and paroxysmal pain. A total intensity score is calculated as the sum of the scores of the 10 descriptors.

12.2.4 Pain Disability Index (PDI)

The PDI [36] measures disability caused by pain in seven areas of daily living (family/home responsibilities, recreation, social activities, occupation, sexual behaviour, self-care, life-support activity). Each item is scored using an 11-point NRS scale (0=No disability, 10=Worst Disability). The total score is employed as the index.

12.2.5 Modified Depression, anxiety and positive outlook scale (DAPOS)

The DAPOS is an 11 item [37] scale, validated for use in patients with chronic non-malignant pain [38]. It overcomes several short-comings of more generic measures of depression. First, it avoids criterion contamination associated with the inclusion of somatic items such as fatigue, weight, and sleep problems, often heavily endorsed by people with pain in relation to the impact of pain. Second, it is developed for people with pain and is designed to be sensitive to the effects of interventions that target pain, rather than depression. Third, it conceptualises positive affect as separate dimension rather than the opposite of negative affect, which may be an important outcome of

treatment for patients without severe depression. Three sub-scales can be derived are derived from DAPOS, and these are

- DAPOS-(D)epression, the score of which is derived from the sum of item 1, 3, 5, 8 and 11
- DAPOS-(A)nxiety, the score of which is derived items from the sum of items 2, 6, and 9
- DAPOS-(P)ositive Outlook, the score of which is derived items derived as the sum of items 4, 7, and 10

12.2.6 Quantitative Sensory Testing [39]

The affected (painful) area for testing for the purpose of the Study will be selected. Its location will be documented.

Mechanical pain sensitivity will be assessed with the following stimuli

1. A set of seven standardized punctate probes, of weights between 8 to 512mN. Each probe would be applied for about 1s, minimum inter-stimulus interval of 10s. The probes are applied first in ascending order and the participant will be asked to indicate when the stimulus (probe) felt just sharp or painful (threshold). The weight at which this occurs would be recorded. Probes of lesser weights are then applied in descending series until the participants indicates that the stimulus is no longer sharp or painful. A total of 5 series (3 ascending, 2 descending) would be employed. **Punctate pain sensitivity** would be calculated as the geometric mean of five thresholds.

2. A standardized soft brush, applied 5 times, each as a single stroke of approximately 2 cm in length over the skin, minimum inter-stimulus interval of 10s. If the stimulus was felt, the participant would be asked to rate how painful the stimulus felt on a '0-100' Numerical Rating Scale ('0' indicating ''no pain'', and '100' indicating ''worst possible pain''). **Dynamic mechanical allodynia** will be calculated as the mean of all the numerical ratings for the brush stimuli.

The baseline scores (and sub scores) are derived from the QST, BPI, ISI, DAPOS, and NPSI, which are completed on the Visit 2.

The endpoint scores (and sub scores) are derived from the same questionnaires completed at Visit 5.

For each questionnaire, the change-from-baseline is calculated as the endpoint score minus the baseline score.

12.3 Exploratory endpoints

DN4 and SF-36 questionnaires are obtained during screening to allow detailed characterisation of the neuropathic pain and its impact of physical and mental health in participants.

Plasma concentrations of ivabradine may be employed to confirm bioavailability of the drug and explain variation in the effect of HCN receptor agonism in individuals.

13 Storage and Analysis of Samples

Blood samples obtained for the screening of individuals would be sent to the Clinical Biochemistry and Haematology laboratories based at the Cambridge University NHS Foundation Trust Hospitals. These bloods are for health screening before enrolment into the Study and will not be anonymised. They would form part of the NHS records, which would allow the GP or relevant clinician to be notified in the event of abnormal and clinically significant results. Results would be reported within 7 days to the researcher, and would be used to help determine the eligibility of the participant. These samples would be discarded once the laboratory analyses are completed.

Blood samples for Ivabradine levels will be centrifuged to extract at least 200µL of serum/plasma, the method employed will be outline in an SOP prior to sample collection. All serum samples will be labelled with the participant's unique Study-specific identifier and collection date only. The serum samples would be transferred for secure storage in a freezer (at -20°C or below) within the Division of Anaesthesia, Addenbrooke's Hospital. These samples would be sent to Argenta Discovery 2009 Ltd, Spire Green Centre, Harlow, UK as a single batch after the final sample from the last participant is acquired. Serum samples will be stored at -80°C on receipt, then analysed in one batch using authentic standards. The samples will be discarded once the laboratory analyses are reported, with the agreement of the Chief Investigator.

14 Statistics

14.1 Statistical methods

There is current uncertainty regarding involvement of HCN channels in maintenance of neuropathic pain. Our Phase I trial (awaiting publication) indicates lack of efficacy of a single dose (15mg) of ivabradine on experimentally-induced pain. However, strong evidence from pre-clinical literature that pain relief requires multiple doses, and is associated with bradycardia (slow heart rate). This single arm, open-label study estimates the likelihood of effect on pain perception when the dose and duration of drug is titrated to achieve a reduction in heart-rate. Blinding here is challenging because of the known effects of the drug on heart rate, which will be monitored both by investigator and participant during this study.

The approach taken here is to only power for biologically significant or clinically useful effects that are unlikely to be explained by placebo-based analgesia. Placebo effects are well established in literature, and has been estimated as a decrease of 6.5mm on a 100mm visual analogue scale in an early meta-analysis of 27 clinical trials in two arms – placebo and arm [40]. A Cochrane meta-analyses in 2004 [41] examined placebo effects in trials that included both a placebo arm, and usual (no treatment arm), and estimated that the placebo-based reduction of pain scores was standardised mean difference (SMD) of -0.25 (95% CI -0.35 to-0.16). This meta-analysis was repeated in 2010 [42], to reveal a SMD of -0.23 (95% CI -0.28 to -0.17). These analyses suggest that placebo-based analgesia achieves modest are on pain (within the context of in other double-blind trials) – about a 1-point reduction on an 11 point NRS. Hence, we choose to power for a greater than 1-point NRS reduction.

This single-arm trial assesses the effect of HCN channel receptor on the daily pain NRS scores. We will use a Bayesian adaptive trial design, similar to designs discussed in Berry et al [43]. This design allows early stopping at an interim analysis if: 1) the involvement of HCN channel receptor in neuropathic pain is highly unlikely (stopping for

'lack of useful biological effect); 2) there is already sufficient evidence that the HCN channel receptor is involved in neuropathic pain (stopping for 'clear and useful biological effect').

The null hypothesis being tested is that the mean reduction in pain score from baseline is less than 1 (or there is a worsening in pain score). The final analysis (if the trial reaches 50 patients) is a t-test of this hypothesis. If the test statistic is less than -2, the null hypothesis will be rejected. Interim analyses will take place after 20, 30, and 40 patients have been assessed. If the trial continues, a final analysis will take place after 50 patients have been assessed.

The Bayesian design involves specifying criteria for stopping early for futility and success. The criteria for early stopping for efficacy will be that the posterior probability that the mean pain score reduction from baseline is greater than 1 is above 0.99. That is the trial will stop early for efficacy if there is overwhelming evidence that the mean reduction in pain score is greater than 1.

For futility stopping, we calculate the predictive probability that the trial will be successful (i.e. the final t-test value would be below -2) if the full sample size of 50 patients are assessed. If this quantity is below 5% (i.e. the chance the trial will end up recommending the treatment is very low), we will stop the trial early for futility. The predictive probability is calculated using the predictive distribution of data from future patients, which is multivariate t. Future patients are simulated (1000 replicates) from this distribution and combined with the real patient data assessed up to that point to calculate a distribution for the predictive t-test.

We have considered the power of the trial under two scenarios. In each we assume the change in NRS score from baseline for each patient can be between -3 and +3, but with different probabilities for each outcome (shown in table below):

Change in pain score from baseline	Probability in null scenario	Probability in alternative scenario
-3	0.15	0.35
-2	0.25	0.25
-1	0.30	0.25
0	0.10	0.05
1	0.05	0.05
2	0.05	0.05
3	0.05	0

These values were chosen so the average change in the null scenario is -1. The average change in the alternative scenario is **-1.65**. This gives a type I error rate of 5.6% and a power of 86.6%. The average number of patents recruited is 28.8 when the null hypothesis is true, and 36.3 when the alternative hypothesis is true.

As a secondary analysis, we will examine the proportion of patients who achieve a greater than 30% reduction in NRS pain score. This is widely considered a minimum clinically important difference (MCID) for analgesic efficacy, and there are data suggesting a reduction of this magnitude is less likely for purely placebo-driven analgesic effect [44].

14.2 Number of Subjects to be enrolled

We plan to enrol between 20 to 50 subjects, depending on interim analyses, replacing any enrolled subject who withdraw, or dropout.

14.3 Criteria for the premature termination of the Study

14.3.1 Study Termination

This Study will be terminated in the event that significant safety concerns are raised, the final decision will be made by the CI, who will act on the recommendation of the Safety Team who will access and review the circumstances surrounding all SAR/SUSAR, or any new and relevant information that comes to light regarding the treatment or study procedures during the study.

14.3.2 Participant Withdrawal

Participants who experience SAR/SUSAR (except for bradycardia) will be withdrawn from the study. The study requires between ten to fifty participants (depending on the interim analysis) to complete. Subjects who withdraw from the study before completion will be replaced.

14.4 Procedure to account for missing or spurious data

All data from all subjects who enrol in the study will be included in the analyses. Missing data will be considered missing at random.

14.5 Definition of the end of the Study

The definition of the end of the Study will be when all Study procedures are completed for the last participant.

15 Data handling and record keeping

15.1 Case Record Forms (CRF)

Paper CRFs will be used to collect source data whenever feasible. Paper CRFs must be completed, dated and signed by the researcher or designee in a timely manner. It remains the responsibility of the researcher for the timing, completeness, legibility and accuracy of the CRF pages.

All paper CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.

The data will be entered into an electronic database. All procedures for the handling and analysis of data will be conducted in accordance with GCP guidelines.

15.2 Source Data

To enable peer review, monitoring, audit and/or inspection the researcher must agree to keep records of all participants (sufficient information to link records e.g., CRFs, hospital records, questionnaires and samples), all original signed informed consent forms and copies of the CRF pages. For this Study the source documents will be the Pain Diaries (a standard operating procedure for a paperless version of the pain diaries

will be generated prior to the commencing the Study), Questionnaires (unless incorporated in CRF), ECG print outs and original Informed Consent Forms.

15.3 Data Protection & Participant Confidentiality

All researchers and Study site staff involved in this Study must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

16 Ethical & Regulatory considerations

16.1 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The researcher must ensure that each Study participant is fully informed about the nature and objectives of the Study and possible risks associated with their participation.

The researcher will obtain written informed consent from each participant before any Study-specific activity is performed. The informed consent form used for this Study and any changes made during the course of this Study, must be prospectively approved by the REC. The researcher will retain the original of each participant's signed informed consent form.

16.2 Ethical committee review

Before the start of the Study or implementation of any amendment, approval of the Study protocol, protocol amendments, informed consent forms and other relevant documents (e.g. advertisements and GP information letters if applicable) will be obtained from the REC. All correspondence with the REC will be retained in the Study Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

16.3 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and HRA.

The only circumstance in which an amendment may be initiated prior to REC and HRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, recruitment of new participants will be halted until the REC and/ HRA approval has been obtained.

16.4 Peer Review

The protocol has been peer reviewed by the Medical Research Council as part of a grant application.

16.5 Declaration of Helsinki and ICH Good Clinical Practice

The Study will be performed in accordance with the spirit and the letter of the Declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

16.6 GCP Training

All Study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this Study. This training should be updated every 2 years or in accordance with the Trust's policy.

17 Sponsorship, Financial and Insurance

The Study will be sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. It is funded by a Medical Research Council programme grant.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical Study caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the Study, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising thorough participation in the clinical Study.

18 Monitoring, Audit & Inspection

The investigator must make all Study documentation and related records available should to allow any inspection by Sponsor representative or other regulatory authority. Should a monitoring visit or audit be requested, the investigator must make the Study documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

19 Protocol Compliance and Breaches of GCP

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol that are found to occur repeatedly will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

20 Publications policy

Ownership of the data arising from this Study resides with the Study team. On completion of the Study the data will be analysed and tabulated and a Final Study Report prepared.

When submitting a paper, article or report for publication it is essential that the NIHR, MRC and CCTU are acknowledged appropriately as well as the type of funding, use of clinical research facilities, fellowship awards, professorship awards, etc.

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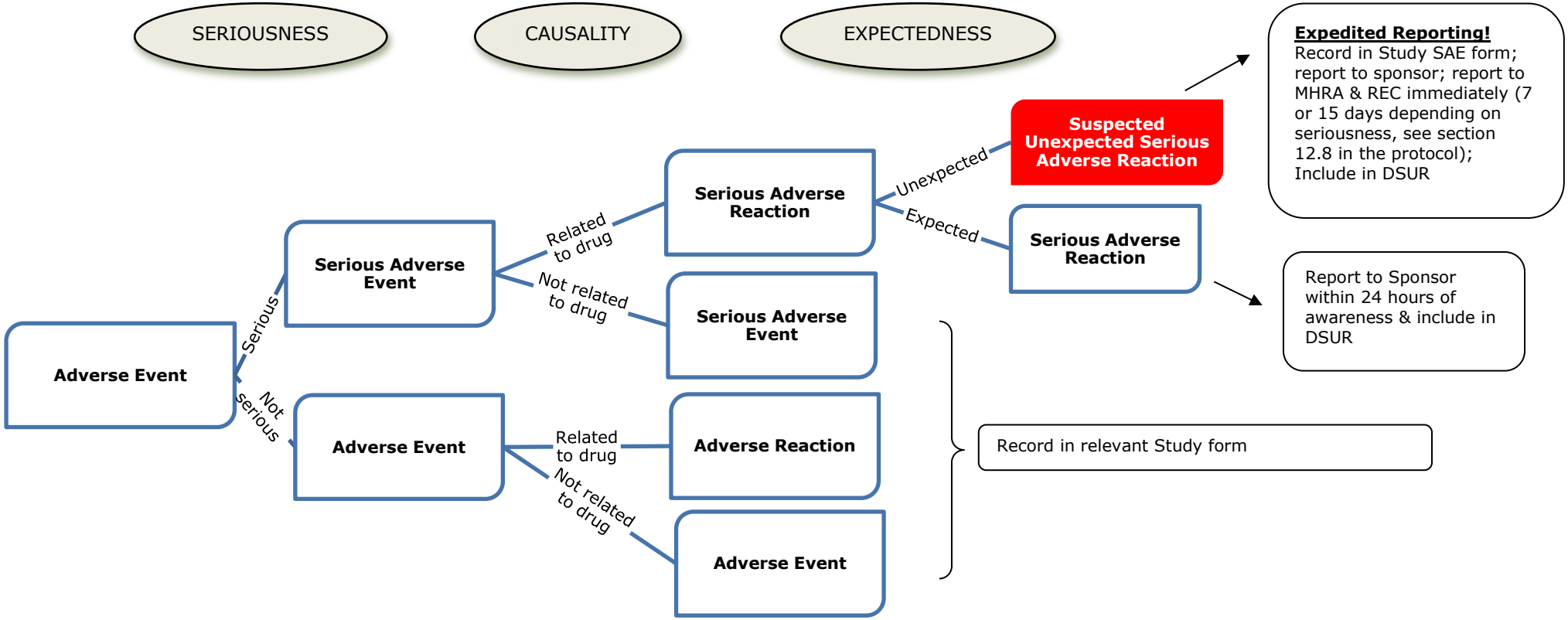
21.1 Appendix 2 - Safety Reporting Flow Chart



21.2 Appendix 3 – Peripheral neuropathic pain diagnoses

Typical peripheral neuropathic pain diagnoses eligible for recruitment.

Patients with painful peripheral neuropathy are diagnosed based on pain localised to distal polyneuropathy (usually in the upper or lower limbs). Characteristics of polyneuropathy includes a decrease in response to pinprick, temperature, vibration or decreased or absent ankle-jerk reflexes.

Patients with post-herpetic neuralgia should have had an eruption of herpes zoster rash not more recently than six months before enrolment, and the rash should have fully resolved at the point of screening

Patients with painful traumatic (post-surgical or accidental) neuropathy and localised pain are eligible provided that the injury is at least 3 months old and clinically healed.

21.3 Appendix 4 – Permitted and Prohibited Concomitant Medication

21.3.1 Prohibited Concomitant Medication

The following section describes the prohibited medications during the study. Patients who are taking or have taken within the last **30 days** prior to screening, any of the following drugs for pain will be excluded from the Study:

- high dose (8%) capsaicin patch
- any skeletal muscle relaxant, including benzodiazepines
- steroids
- mexiletine
- dextromethorphan
- amantadine
- memantine
- baclofen
- cannabinoids
- any antipsychotic or neuroleptic medications
- monoamine oxidase inhibitors or any other antidepressants not included in the list below of Permitted Concomitant Medications with Restrictions
- any other medication used for pain that are deemed by the clinical researcher to affect Study safety and outcome

21.3.2 Permitted Concomitant Medication with Restrictions

The following section describes the medications allowed with restrictions during the study.

Patients will be allowed to take no more than two drugs from **the following medication classes for managing their neuropathic pain**, provided that the dosage(s) have remained unchanged for at least **30 days** prior to the Screening visit (Visit 1):

- any tricyclic antidepressant (e.g., amitriptyline, imipramine, nortriptyline, desipramine)
- any anticonvulsant (e.g., gabapentin, pregabalin, carbamazepine, phenytoin, valproic acid)
- any one of the following serotonin-norepinephrine reuptake inhibitors (SNRIs); duloxetine, or venlafaxine
- tramadol, or tapentadol, or any one opioid analgesic via oral or transdermal route only.
- topical treatment (including lidocaine plaster, low-concentration (<=0.075%) capsaicin)

Patients will be allowed to take the following medications for other indications throughout the Study:

- SSRI for depression at stable dosages
- oral aspirin (≤ 325 mg/day) for cardio-protection
- an oral NSAID for management of osteoarthritis at stable dosages

Patients will be allowed to take up to 4 grams daily of paracetamol/acetaminophen for unacceptable pain during the Study.

21.4 Appendix 5 – Creatinine Clearance (Cockcroft-Gault formula)

$$\text{Creatinine Clearance (mL/min)} = \frac{N \times [140 - \text{age (years)}] \times \text{weight}^* \text{ (kg)}}{\text{Serum creatinine (micromol/L)}}$$

Where N = 1.23 for males, 1.04 for females

* Use ideal body weight (IBW) if actual weight is greater than 120% IBW

IBW (kg) = 0.9 x height (in cm) – 88 (males) or 92 (females)