Targeted heart rate control using the funny current inhibitor ivabradine to reduce morbidity in patients undergoing non-cardiac surgery: a phase IIa, triple blind, placebo controlled randomised trial

Short Title	FUNNY trial
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1. CONTENTS

2. GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ABP	Ambulatory Blood Pressure
APR	Annual Progress Report
BP	Blood Pressure
CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
eCRF	Electronic Case Report Form
EOT	End of Trial
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
NT-proBNP	N-terminal pro-B-type natriuretic peptide
Participant	An individual who takes part in a clinical study
PI	Principal Investigator
PIS	Patient Information Sheet
POMS	Postoperative Morbidity Survey
QMUL	Queen Mary University of London
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WHRI	William Harvey Research Institute

3. SIGNATURE PAGE

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: Professor Gareth Ackland

Chief Investigator affiliation: Queen Mary University of London

Signature and date: Gareth Ackland Digitally signed by Gareth Ackland Date: 2025.11.14 09:10:23 Z

Statistician Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician name: Jackie Cooper

Statistician affiliation: Queen Mary University of London

Signature and Date: Jackie Cooper Digitally signed by Jackie Cooper Date: 2025.11.14 09:40:27 Z

Principal Investigator Agreement

The clinical study as detailed within this research protocol, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator name:

Principal Investigator affiliation:

Signature and date:

4. SUMMARY AND SYNOPSIS

Full title	Targeted heart rate control using the funny current inhibitor ivabradine to reduce morbidity in patients undergoing non-cardiac surgery: a phase IIa, triple blind, placebo controlled randomised trial
Short title	FUNNY
Trial design and methodology	Phase IIa, triple blind, placebo controlled randomised trial
Phase of the trial	Phase IIa
Study duration	55 months
Study setting	Hospitals undertaking elective or urgent non-cardiac surgery in participating countries
Investigational medicinal product	Ivabradine
Medical condition or disease under investigation	Patients aged 55 years and over undergoing elective or urgent non-cardiac surgery
Number of patients	350 patients (175 patients per treatment arm)
Primary outcome measure	The primary outcome is a composite of myocardial injury associated with morbidity within seven days of surgery. To meet the criteria for the primary outcome, the patient must experience both of the following: 1. Increase in serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) concentration of: a. An absolute value of ≥15ng L-1 on day one, day two or day three after surgery OR b. An increase of ≥5 ng L-1 from the preoperative value on day one, day two or day three after surgery when the preoperative value was ≥15ng L-1 AND 2. Any POMS defined morbidity domain on day three or day seven after surgery.
Maximum treatment duration	Three days
Follow-up duration	180 days from the day of surgery
End of trial definition	When the last patient has completed their 180-day follow-up

5. PROTOCOL CONTRIBUTORS

The Sponsor and funders have not played, nor will play a role in the study design, conduct, data analysis and interpretation, manuscript writing, and/or dissemination of results.

The Sponsor and funder did not control the final decision regarding any aspects of the trial.

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6. INTRODUCTION

6.1. High-risk surgical population

Surgical patients with multi-morbidity who are most at risk of postoperative complications have profound parasympathetic dysfunction, as evidenced by higher resting heart rate,[11-14] slower heart rate recovery after exercise[15] and impaired heart rate variability/arterial baroreflex regulation.[8-10] These patients are characterised by poor exercise capacity and elevated levels of systemic inflammation.[1-11] In particular, patients with cardiac vagal dysfunction,[12] as quantified by higher resting heart rate and delayed heart rate recovery after exercise-testing,[3] are at particularly elevated risk of postoperative complications. Preoperative impairment of parasympathetic (vagal) autonomic function is a sole predictor of perioperative myocardial injury, postoperative infections and death.[15]

Notably, in the general population, loss of cardiac vagal activity as quantified by impaired heart rate recovery after exercise, is an independent, robust predictor of cardiovascular morbidity and all-cause mortality.[13] [14] In part, this reflects the essential role of the vagus nerve in optimising exercise capacity.[15] [16, 21, 22] In health, cardiac parasympathetic function is regulated by the arterial baroreflex.[7] [8] However, impairment of the arterial baroreflex and loss of brainstem cardiac vagal activity are pathognomonic features triggered by systemic inflammation and treatment occurring as a consequence of (surgical) tissue injury.[7-9] Impaired neuro-cardiovascular control, which can be tested for before surgery by orthostatic testing[17], contributes to intraoperative hypotension, which is repeatedly associated with adverse outcomes.[5]

These perioperative data mirror the cardiac failure literature, where patients with cardiac vagal dysfunction have the worst prognostic endotype.[18] Taken together, these data show that patients with features of subclinical parasympathetic autonomic dysfunction are most likely to sustain myocardial injury and die after non-cardiac surgery, representing a distinct endotype that can be targeted by precision medicine.

6.2. Heart rate and cardio-protection

Troponin release is most common in patients with key features of the physiological phenotype of subclinical heart failure.[1-9] Slower heart rates is clearly associated with cardio-protection in patients with cardiac failure[19] [20] and perioperative patients.[2] [5] [6] [21] However, lowering heart rate in the perioperative setting through cardio-specific beta-blockade results in higher overall mortality.[22] This is because the physiological features of surgical patients at highest perioperative risk (i.e. low exercise capacity) are incompatible with the rapid introduction of

high-dose beta-1 blockade, which would predictably cause hypotension and impair cardiac output.[5] The limited time that is available before surgery, coupled with the deconditioned state of patients, present significant barriers to therapy. Because putative interventions [e.g. exercise] require months to improve (to a highly variable extent) cardiorespiratory-autonomic pathophysiology,[23] there is an urgent need to: (a) understand the perioperative pathophysiology of these higher-risk individuals; (b) examine rational, stratified and targeted interventions based on that enhanced mechanistic understanding.

6.3. Selective heart rate lowering to reduce morbidity after non-cardiac surgery

Sustained exercise training reduces resting heart rate via downregulation of the funny channel HCN4,[24] which regulates the funny (I_f) current in the sinoatrial node by producing hyperpolarization-activated currents.[25] These data suggest strongly that, in deconditioned, physically unfit patients with cardiac vagal dysfunction, inhibiting the funny channel HCN4 should be beneficial through targeted reduction in heart rate over the perioperative period. Crucially, ivabradine slows heart rate by specifically inhibiting the I_f current in the sinoatrial node but does not impair myocardial contractility, affect blood pressure or impair sympathetic nervous activity, even in patients with cardiac failure.[26] At therapeutic concentrations, ivabradine has no action on other channels in the heart or vascular system.[26] Ivabradine is indicated in moderate to severe chronic heart failure (New York Heart Association class II to IV) with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. The SHIFT trial in patients with heart failure found that ivabradine reduced hospital admissions for worsening heart failure (672 [21%] placebo *vs* 514 [16%] ivabradine; hazard ratio 0.74 (95%CI:0.66–0.83; p<0.001), as well as deaths attributable to heart failure (151 [5%] *vs* 113 [3%]; hazard ratio 0.74 (95%CI:0.58–0.94), p=0.014).[19] Importantly, in this high-risk population, fewer serious adverse events (SAEs) occurred in the ivabradine group with a low risk of symptomatic bradycardia.

6.4. Dosing of Ivabradine

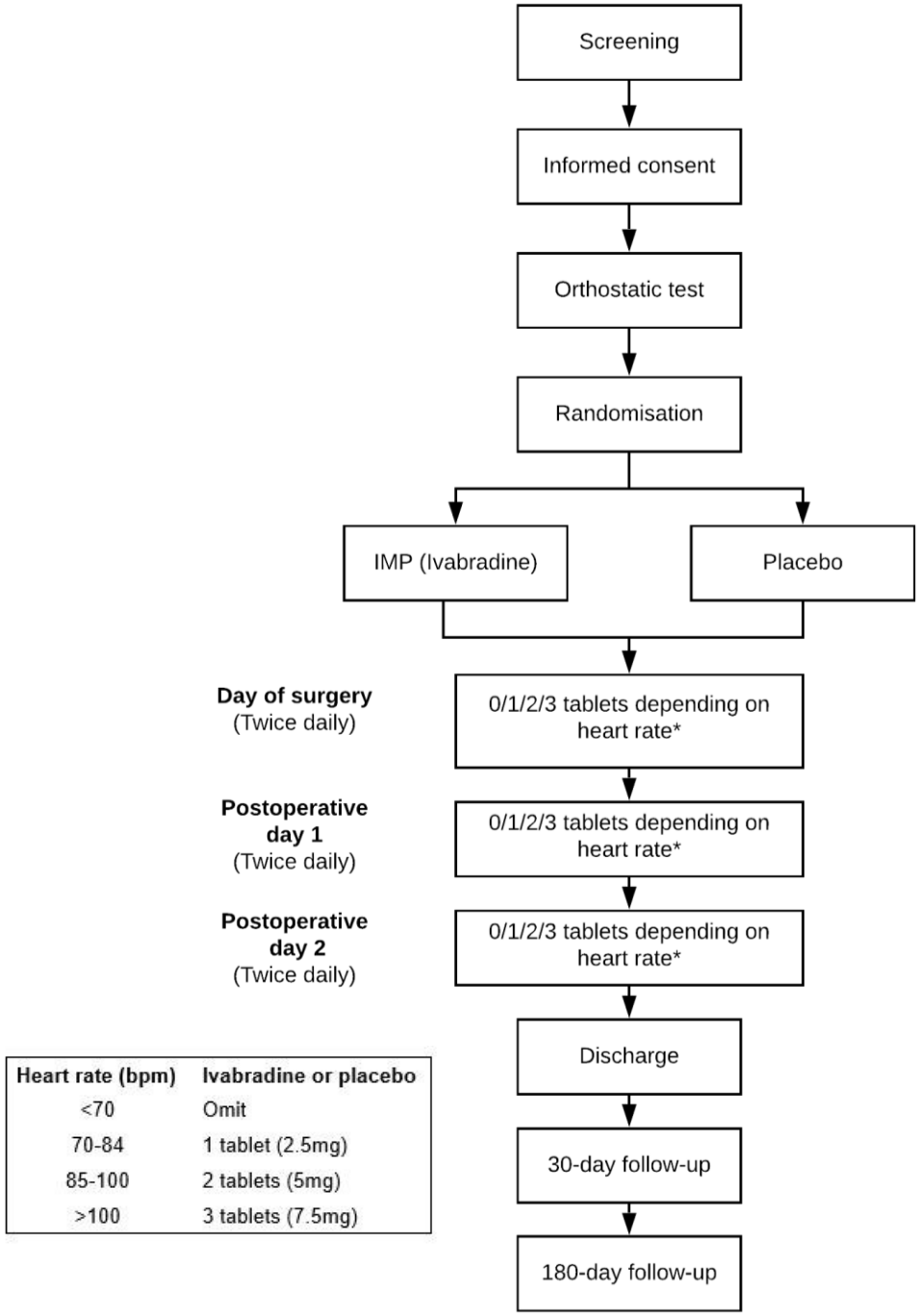
The dose of ivabradine will be administered in accordance with the patient's baseline heart rate. Patient's will be administered either no IMP, 2.5mg, 5mg or 7.5mg of IMP. This is a modification of the Summary of Product Characteristics (SMPC), appendix D, that primarily refers to the administration of ivabradine in patients with stable cardiac failure, which is essentially in an outpatient (unmonitored) setting. In contrast patients enrolled in the FUNNY trial will be inpatients during the intervention and will be monitored throughout their hospital stay. A recently published meta-analysis investigating the effects of ivabradine on

cardiovascular events and mortality in critically ill patients looked at data from 14 randomised controlled studies on ivabradine.[27] The patients included in the meta-analysis have a greater burden of disease and are more clinically unstable than the surgical patients we propose to enrol in the trial and administer ivabradine. 10 out of these 14 trials have used the same study design as we are proposing which is a placebo-controlled trial. Notably, 11 out of the 14 trials were conducted in patients who had unstable cardiac function due to acute heart failure which is an exclusion criteria in this trial. All these studies used doses that were titrated to heart rate including up to 7.5mg twice per day. Slow heart rate (bradycardia) and other adverse events were similar between placebo and ivabradine. There were 25 (10.3%) episodes of bradycardia in the ivabradine arm and 17 (8.8%) in the control arm with no evidence of a difference between groups (five RCTs, *n*=434; OR=1.2; 95% CI, 0.60–2.38; *P*=0.61). These data summarised in the meta-analysis demonstrate the safety of ivabradine in a more unstable population than that proposed for the FUNNY trial.

6.5. Rationale

The rationale of this study is to demonstrate that targeted lowering of heart rate during the perioperative period reduces myocardial injury and morbidity for patients after elective or urgent non-cardiac surgery.

7. TRIAL FLOWCHART



Heart rate (bpm)	Ivabradine or placebo
<70	Omit
70-84	1 tablet (2.5mg)
85-100	2 tablets (5mg)
>100	3 tablets (7.5mg)

*please see section for trial dosing for further details

8. TRIAL OBJECTIVES AND DESIGN

8.1. Primary objective

To determine whether the targeted lowering of heart rate with ivabradine during the perioperative period reduces morbidity associated myocardial injury within seven days of elective or urgent non-cardiac surgery.

8.2. Secondary objective

To examine the relationship between selective heart rate reduction and severity of Clavien-Dindo graded complications and postoperative morbidity survey (POMS) defined morbidity.

8.3. Primary outcome measures

The primary outcome is a composite of myocardial injury associated with morbidity within seven days of surgery.[28] To meet the criteria for the primary outcome, the patient must experience the following:

1. Increase in serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) concentration of:
    a. An absolute value of ≥15ng L^{-1} on day one, day two or day three after surgery
    OR
    b. An increase of ≥5 ng L^{-1} from the preoperative value on day one, day two or day three after surgery when the preoperative value was ≥15ng L^{-1}

    AND
2. Any POMS defined morbidity domain on day three or day seven after surgery (see appendix B for definitions)

8.4. Secondary outcome measures

1. Increase in serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) concentration of:
    a. An absolute value of ≥15ng L^{-1} on day one, day two or day three after surgery
    OR
    b. An increase of ≥5 ng L^{-1} from the preoperative value on day one, day two or day three after surgery when the preoperative value was ≥15ng L^{-1}
2. Any POMS defined morbidity domain on day three or seven after surgery (see appendix B for definitions)
3. Absolute levels of serum high-sensitivity troponin-T (Elecsys, Roche Diagnostics) measured on day one, day two and day three after surgery
4. Mortality within 180 days from surgery

5. Predefined complications at day 30 after surgery graded using the Clavien-Dindo classification*

*defined according to clinical criteria, see appendix C

8.5. Process measures

1. Duration of hospital stay from surgery (number of calendar days from surgery until hospital discharge)
2. Number of calendar days requiring critical care admission (level two and three) up to 30 days from surgery*

*level of care defined in appendix C

8.6. Assessment of primary and secondary outcomes

Additional blood samples will be collected to measure the primary and secondary outcome measures. Serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) levels will be measured in blood samples collected on the day of surgery before the induction of anaesthesia and on days one, two and three after surgery. The investigator making the assessment for POMS and Clavien-Dindo graded complications should not have been involved in the patient's care and should be unaware of their treatment group allocation. This assessment will be based on clinical data including information from patients' medical records, including (but not limited to) microbiology test results, blood test results, drug prescription charts, radiology tests etc. Patients discharged from hospital before day 30 will be contacted shortly after day 30 to ascertain whether they have received any new treatment or if they have been re-admitted to hospital or seen a doctor since discharge. For patients who have received further treatment or seen a health professional since discharge, further details will be collected directly from the hospital/general practitioner (GP) or from the patient's health records. Patients' mortality status will be confirmed at 180 days from surgery.

When assessing either POMS or Clavien-Dindo complications, if the initial assessment by a research associate is 'no complication', then the patient's outcome is classified as 'none'. If the initial assessment is a 'complication', then this decision must be confirmed by the site Principal Investigator (PI). The PI's can either confirm the research associate's initial assessment of 'complication' (in which case the patient's outcome is classified as 'complication'), or they can refute it (in which case the patient's outcome is classified as 'none'). The PI should only undertake this evaluation if they are unaware of the patient's treatment group allocation. If they are aware of the treatment allocation, they should delegate this evaluation to a nominee who is unaware of treatment group allocation. The nominee should

be a senior clinician. The secondary clinical outcomes will be assessed using a similar approach as for the primary outcome.

9. TRIAL METHODOLOGY

9.1. Study design

Phase IIa, triple blind, placebo controlled randomised trial.

9.2. Study setting

The study will take place in the UK and Switzerland. The list of all participating sites can be found at the beginning of the protocol.

9.3. Eligibility criteria

All patients must meet all of the inclusion criteria and none of the exclusion criteria listed below.

9.3.1. Inclusion criteria

- Patients aged 55 years and over [28]
- Undergoing elective or urgent non-cardiac surgery requiring general and/or regional anaesthesia with sedation, expected to take longer than 120 minutes from the induction of anaesthesia
- At least one medical risk factor for perioperative myocardial injury (see appendix A)
- History of hypertension (requiring anti-hypertensive drug) or hypertension recorded in pre-assessment clinic [BP>140mmHg systolic; >90 mmHg diastolic]

9.3.2 Exclusion criteria

- Inability or refusal to provide informed consent
- Patients lacking capacity
- Patients with atrial fibrillation (persistent/ chronic or paroxysmal)
- Prior use of ivabradine within the previous 30 days
- Current participation in a clinical trial of a treatment with a similar biological mechanism
- Previous enrolment into FUNNY trial
- Contraindication to ivabradine (see appendix D)
- History of hypersensitivity or allergy to ivabradine or any of its excipients (see appendix D)
- Women of childbearing potential* (this includes pregnancy and lactation)

*A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant unless permanently sterile.

10. TRIAL PROCEDURES

10.1. Conducting trial procedures during the Covid-19 pandemic

The safety of the trial participants is paramount. Patients enrolled in the trial are unlikely to face any additional risks to COVID-19 compared with those who are not part of the trial. For example all study related procedures will be conducted during the patient's hospital visits and during their stay that are part of their routine care and no additional visits will be required. The safety of research staff is also extremely important and they would need to complete any necessary risk assessments required by their employers.

Local Trust policy, MHRA guidelines and NIHR re-start framework will always be followed by researchers when conducting trial procedures to ensure the appropriate safeguards are in place for themselves and the participants. This will include using different approaches for trial delivery such as using digital elements to speak with patients, data collection and monitoring. Hosting the trial at hospital sites will not pose any additional risks to participants, staff and the organisation or the general proliferation of the disease.

10.2. Participant identification and screening

Potential participants will be screened for eligibility by a member of the research team at the site, having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff. In this trial a member of the research team will be considered part of the direct care team. All patients that undergo screening and meet the inclusion criteria will be recorded on the screening log. Only anonymised screening data will be collected by the central trial coordinating team for publication purposes. Once the patient has been randomised they will be recorded on the study enrolment log.

10.3. Informed consent procedures

The consent process will take place face to face or via a locally approved electronic method (phone, video conferencing etc.). All potential participants will be provided with a copy of the patient information sheet (PIS) and informed consent form (ICF) together with an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. This will be done either in person, via email or by post. The patients will also be given the opportunity to ask questions about the study. For patients who are consented to participate in the trial a copy of the PIS and signed ICF will be filed in the medical notes. Patients who are consented but not

entered into this study should be recorded (including reason not entered) on the screening log in the Investigator Site File (ISF). Original signed consent forms will be kept by the investigators and a copy will be given to the participant. A letter will also be sent to the GP informing him/her of the trial and the participant's involvement in it.

All patients will be given a minimum of 24 hours between the time they are approached about the study and the time when consent is given. For those patients who have not been contacted face-to-face, the signed consent form will be returned via email or by post. If the patient has signed the consent form before the day of surgery, consent will be verbally confirmed before randomisation. If any further safety information arises, which may result in significant changes in the risk/benefit analysis, the PIS and ICF must be reviewed and if applicable updated accordingly.

10.4. Responsibility for obtaining consent

At each site it is the responsibility of the PI or appropriately trained delegate, i.e. research nurse, to obtain consent from each subject prior to participation in this trial. If consent is not taken by a medically qualified person, the PI or delegated doctor will countersign the ICF afterwards in a timely manner. All staff taking consent will be trained in taking consent and this will be evidenced on the on the delegation log. They will also have appropriate Good Clinical Practice (GCP) training. If for some reason an investigator is not available in person or by phone and the participant wishes to speak with them before providing consent, a second consent visit should be arranged. The eligibility confirmation and consent process will be documented in the medical records.

10.5. Consent considerations

The right of a participant to refuse participation without giving reasons will be respected. The participant remains free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, for example if during the trial new research safety information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a participant, the PI will ensure this is done in a timely manner.

10.6. Written/ reading / translation considerations

Patients who do not have the ability to understand the language used in the PIS will be provided with a translator.

11. BLINDING

This is a triple blind trial. The trial participants, healthcare staff administering the treatment and the statistician will be blinded to the treatment group allocation. Primary outcome will be analysed by individuals masked to the patient treatment allocation and clinical outcomes. To maintain blinding, placebo and ivabradine tablets will be identical (IMP supply arranged by MODEPHARMA). Placebo film-coated tablets will be developed and manufactured to match the appearance (shape, dimensions and colour) of a commercially available generic ivabradine 2.5mg film-coated tablet. The placebo tablets will contain no ivabradine-containing ingredients. Each IMP pack will be labelled with a unique kit number to maintain blinding.

The Joint Research Management Officer at Queen Mary University of London will be unblinded to facilitate unblind SUSAR reporting to the MHRA.

11.1. Unblinding

Since blinding is critical to the integrity of the trial, unblinding a participant's treatment is strongly discouraged. However, it is understood that on rare occasions unblinding will be required (e.g. for medical or safety reasons if it will alter clinical management). For the purposes of this trial, if a patient experiences refractory bradycardia (see appendix C for definition), unblinding will be required. The rescue treatment should not depend on the treatment group allocation, so unblinding requests are expected to be rare. If the emergency is clearly not related to the IMP, the problem may be appropriately managed by assuming that the participant is receiving highest possible dose of ivabradine (7.5mg), without the need for unblinding. Where unblinding is being considered, the PI (or assigned delegate) should have determined that the information is necessary, i.e. that it will alter the participant's immediate management. Site teams are encouraged to contact the study coordinating team (admin@funnytrial.org) if they wish to discuss this further, but they will always have the ability to unblind via the trial database.

Treatment identification information should be kept confidential and should be disseminated only to those individuals involved with the medical management of the participant. The CI will be kept informed of all instances of unblinding but should remain blinded to treatment allocations them self. The trial manager and the site staff will maintain a record of all unblinding events including: patient trial ID, the date code break was performed, the person who broke the blind, and reason for it. The breaking of the code and the reasons for doing so will also be captured on the electronic case report form (eCRF), in the site file and medical notes. The code break for the trial will be held by the trial coordinator until the end of the trial when it will

be filed in the Trial Master File (TMF). The CI will ensure any unblinding is documented at the end of the study in any final study report and/or statistical report. The information will also be disseminated to the Data Monitoring and Ethics Committee (DMEC) for review in accordance with the DMEC Charter.

12. TRIAL INTERVENTION

12.1. Orthostatic test

After the participant has provided written informed consent, but before randomisation they will undertake an established orthostatic test, whilst having their heart rate recorded.[29] This will be conducted by a suitably trained investigator. The test will require the heart rate being recorded while the participant is sitting in a chair in a quiet room for three minutes before standing up for three minutes. The completion of the test will be documented in the patients' medical records.

12.2. Allocation method

Randomisation will occur on the day of surgery but before the surgery is due to start. Before randomisation consent must be obtained and it must be confirmed with the lead anaesthetist and/ or surgeon on the day of surgery that the procedure will go ahead. Participants will be centrally allocated to treatment groups in a 1:1 ratio by minimisation with a random component. Minimisation variables are:

(1) surgical procedure category (surgery involving the gut *OR* all other surgery)

(2) trial site

Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. The allocation sequence is generated by an automated algorithm and is concealed to all trial investigators. The system for generating the allocation sequence will be bespoke and will be developed in–house. The system will be validated for use by the trial statistician.

12.3. Allocation procedure

To enter a patient into the trial, research staff at the site will log on to a web-based randomisation and data entry platform hosted by Queen Mary University of London (QMUL) and complete the patient's details to obtain a patient specific trial ID and IMP kit number. A confirmation email containing the trial ID and IMP kit number will be automatically sent by the system to the person who randomised the patient. This email will be printed and filed in the

ISF. For each patient, IMP tablets will be dispensed from the same kit on the day of surgery (preoperatively and postoperatively) and on postoperative days one and two.

12.4. Drug intervention

The trial intervention will start on the day of surgery before the induction of anaesthesia and continue on postoperative day one and day two (unless systolic BP is <90mmHg or MAP is <60mmHg or new onset arrhythmia). Patients will receive either ivabradine or placebo twice daily from the allocated IMP kit with a 12-hour (± 2 hours) gap in-between the administrations. Treatment breaks are not permitted. The number of tablets per dose is dependent on the heart rate recorded within one hour before dosing. If no measurements are available, heart rate will be measured before drug administration. If multiple measurements have been recorded within one hour before dosing, the lowest value will be taken to consider the dose of IMP. The tablets should be administered orally by a medically qualified person and documented in the medical notes, according to the following schematic:

Heart rate (bpm)	Ivabradine or placebo
<70	Omit
70-84	1 tablet (2.5mg)
85-100	2 tablets (5mg)
>100	3 tablets (7.5mg)

Treatment will continue for a maximum of three days, or less if the patient is discharged. If any doses are missed, unless a patient is discharged; or an incorrect number of tablets are given a protocol deviation should be entered. Tablets will be crushed for delivery via nasogastric (NG) tube on the few occasions when patient may be unable to swallow after surgery (e.g. after some gastrointestinal surgery).

12.5. Trial blood sample collection

Blood samples (approximately 15ml) will be collected on the following time points: preoperatively before induction of anaesthesia and on days one, two and three after surgery. Where possible, these samples will be taken at the same time as when blood samples required for routine clinical care are obtained.

12.6. Continuous heart rate and blood pressure monitoring

At selected centres, we will measure heart rate using a Holter monitor and blood pressure using an ambulatory blood pressure monitor cuff. The patient will wear these monitors for at least one hour before induction of anaesthesia up to three days postoperatively. Patients

should wear the monitor for a minimum of four hours per day. The Holter monitor, blood pressure cuff and monitor will be loaned to the sites by the Sponsor.

12.7. Trial schedule

12.7.1. Schedule of treatment for each visit

The trial intervention period will commence on the day of the orthostatic test and finish with the 180-day follow-up.

12.7.2. Schedule of assessment

Event/Visit	Screening	Pre-assessment	Day of surgery (preop)	Day of surgery (postop)	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5	Postop day 7	Hospital discharge	Follow-up 30 days post randomisation	Follow-up 180 days post randomisation
Inclusion/exclusion - blood measure review[1]	X												
Heart rate and blood pressure safety review	X		X	X	X						X		
Informed consent		X	X[2]										
Orthostatic test		X[3]	X[3]										
Heart rate[4]			X	X	X	X	X						
Blood pressure[4]			X	X	X	X	X						
Randomisation			X										
Medical record review including POMS score	X	X	X	X	X	X	X			X	X	X	X
Collection of trial blood sample[5]			X		X	X	X						
Follow-up phone call							X[6]	X[6]	X[5]			X[6]	
Review of AE/SAE		X	X	X	X	X	X[6]	X[6]	X[6]		X[6]	X[6]	
Administration of IMP/placebo			X	X	X	X							

[1] *potassium, sodium creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin.*
[2]consent should be verbally re-confirmed on the day of surgery if obtained previously
[3]can be done after written informed consent during pre-assessment clinic OR before the operation on the day of surgery
[4]at some centres additional measurements to standard of care will be collected of heart rate using a holter monitor and blood pressure using a blood pressure cuff. This is collected specifically for trial purposes only
[4]blood samples are for study purposes only for Troponin-T and NT-proBNP measurements
[5]for safety reasons all patients will be followed-up daily until day 30 of their follow-up

12.8. Trial assessments

The following data will be collected from all patients:

Randomisation data

- Initials
- Date of consent and surgery
- Age
- Gender
- Checklist to ensure the patient meets the eligibility criteria
- Planned surgical procedure category (surgery involving the gut, all other surgery)
- Trial ID (generated automatically at the point of randomisation)

Baseline data

- Ethnic background
- Orthostatic test (see section 12.1)
- Co-morbidities
- Smoking status (within the last 14 days)
- Cardiovascular medications
- Height
- Weight
- Ethnicity (to calculate estimated glomerular filtration rate)
- Laboratory data (haemoglobin, creatinine, neutrophil count, lymphocyte count, albumin)
- Pre-operative resting heart rate and rhythm one hour before IMP administration
- Number of IMP tablets administered before surgery
- Time of IMP administration
- Continuous heart rate (measured with Holter monitor/telemetry)[1]
- Continuous blood pressure (measured with ABP/telemetry)[1]
- Planned level of care on the first night after surgery
- AE/SAE review

[1]selected sites only

During surgery

- Start and end times of surgery
- Surgical procedure category (surgery involving the gut, all other surgery)

- Surgical technique (open, laparoscopic or laparoscopic assisted, laparoscopic converted to open)
- Anaesthetic technique (general anaesthesia, epidural, spinal, other regional anaesthesia, sedation)
- Endotracheal intubation for surgery
- Arrhythmias
- Volume of blood products administered (packed red cells, all other products)
- Continuous heart rate (measured with Holter monitor/telemetry)[1]
- Continuous blood pressure (measured with ABP/telemetry)[1]
- Systolic blood pressure <90mmHg (Y/N, lowest value, duration, IV fluids, pressor treatment [e.g. phenylephrine, ephedrine, metaraminol, norepinephrine])
- Heart rate >100bpm (Y/N, highest value, duration, IV fluids, drug treatment)
- AE/SAE review

[1]selected sites only

Postoperative period

- Arrhythmias
- Creatinine measurement
- Volume of blood products administered (packed red cells, all other products)
- Urine output
- Systolic blood pressure <90mmHg (Y/N, lowest value, duration, IV fluids, pressor treatment [e.g. phenylephrine, ephedrine, metaraminol, norepinephrine])
- Heart rate >100bpm (Y/N, highest value, duration, IV fluids, drug treatment)
- Rescue treatment for bradycardia since the previous dose
- Resting heart rate and rhythm one hour before IMP administration
- Number of IMP tablets administered
- Time of IMP administration
- Actual level of care on the first night after surgery
- Continuous heart rate (measured with Holter monitor/telemetry)[1]
- Continuous blood pressure (measured with ABP/telemetry)[1]
- AE/SAE review

[1]selected sites only

Postoperative day one

- Arrhythmias

- Volume of blood products administered (packed red cells, all other products)
- Urine output
- Blood sample
- Cardiovascular medications
- Level of care on the second night after surgery
- Systolic blood pressure <90mmHg (Y/N, lowest value, duration, IV fluids, pressor treatment [e.g. phenylephrine, ephedrine, metaraminol, norepinephrine])
- Heart rate >100bpm (Y/N, highest value, duration, IV fluids, drug treatment)
- Laboratory values (haemoglobin, creatinine, neutrophil count, lymphocyte count, albumin)
- Rescue treatment for bradycardia since the previous dose[2]
- Resting heart rate and rhythm one hour before IMP administration[2]
- Number of IMP tablets administered[2]
- Time of IMP administration[2]
- Continuous heart rate (measured with Holter monitor/telemetry)[1]
- Continuous blood pressure (measured with ABP/telemetry)[1]
- AE/SAE review
- Hospital discharge on postoperative day one

[1]selected sites only

[2]recorded twice daily

Postoperative day two

- Arrhythmias
- Volume of blood products administered (packed red cells, all other products)
- Urine output
- Blood sample
- Cardiovascular medications
- Systolic blood pressure <90mmHg (Y/N, lowest value, duration, IV fluids, pressor treatment [e.g. phenylephrine, ephedrine, metaraminol, norepinephrine])
- Heart rate >100bpm (Y/N, highest value, duration, IV fluids, drug treatment)
- Laboratory values (haemoglobin, creatinine, neutrophil count, lymphocyte count, albumin)
- Rescue treatment for bradycardia since the previous dose[2]
- Resting heart rate and rhythm one hour before IMP administration[2]
- Number of IMP tablets administered[2]

- Time of IMP administration[2]
- Continuous heart rate (measured with Holter monitor/telemetry)[1]
- Continuous blood pressure (measured with ABP/telemetry)[1]
- AE/SAE review
- Hospital discharge on postoperative day two

[1]selected sites only

[2]recorded twice daily

Postoperative day three

- Arrhythmias
- Volume of blood products administered (packed red cells, all other products)
- Urine output
- Blood sample
- Cardiovascular medications
- Systolic blood pressure <90mmHg (Y/N, lowest value, duration, IV fluids, pressor treatment [e.g. phenylephrine, ephedrine, metaraminol, norepinephrine])
- Heart rate >100bpm (Y/N, highest value, duration, IV fluids, drug treatment)
- Laboratory values (haemoglobin, creatinine, neutrophil count, lymphocyte count, albumin)
- Continuous heart rate (measured with Holter monitor/telemetry)[1]
- Continuous blood pressure (measured with ABP/telemetry)[1]
- AE/SAE review
- Hospital discharge on postoperative day three
- POMS (see appendix B)

[1]selected sites only

[2]recorded twice daily

Postoperative day four to five

- AE/SAE review

Postoperative day seven

- POMS (see appendix B)
- AE/SAE review

Hospital discharge

- Blood pressure (last three measurements before discharge)
- Heart rate (last three measurements before discharge)
- AE/SAE review

Follow-up data

30-day follow-up

- Date of follow-up
- Mortality status within 30 days of surgery
- Clavien-Dindo graded cardiac complications within 30 days of surgery
- Clavien-Dindo graded respiratory complications within 30 days of surgery
- Clavien-Dindo graded infective complications within 30 days of surgery
- Other predefined Clavien-Dindo graded complications within 30 days of surgery
- Acute kidney injury (using KDIGO staging criteria)
- Additional treatments
- Patients admitted to a critical care unit
- Number of days in level two and level three critical care within 30 days of surgery
- Duration of primary hospital admission
- Re-admission to hospital within 30 days of surgery
- Blinding status
- AE/SAE review

180-day follow-up

- Date of follow-up
- Mortality status within 180 days of surgery

Supplementary forms:

- Withdrawal
- AE/SAE
- Protocol deviation
    - Incorrect dose given
    - Missed dose
    - Other deviation

12.9. Withdrawal criteria

All study participants are free to withdraw from the study at any time. Any patient who is withdrawn from the trial or withdrew consent at any time after randomisation but before the last follow-up visit is considered an early withdrawal. This will be documented in the eCRF and medical notes. A complete set of data up to the time of withdrawal including the reason for withdrawal will be collected for every patient who withdraws consent. All randomised patients will be included in the final analysis on an intention to treat basis.

12.10. Withdrawal from trial treatment

It is expected that on some occasions continuing to receive the IMP is no longer in the participant's best interests. In these cases the PI should withdraw a participant from the trial treatment. Some of the reasons for discontinuing the treatment may include:

- two measurements of heart rate below 50 bpm taken 10 minutes or more apart.
- any measurement of systolic blood pressure < 90 mmHg or diastolic < 50 mmHg
- clinically significant arrhythmia
- pregnancy
- use of a prohibited therapy (please see section on concomitant therapy)
- the occurrence of an AE/SAE
- unrelated medical illness or clinical conditions representing a potential risk - at the judgment of the investigator
- a patient's own request to end treatment

If a patient is withdrawn from the treatment for any reason, the patient remains in the trial and is followed up as per protocol unless the patient specifically asks not to be contacted for further follow-up. In this case the data will be collected from the medical records unless the patient specifically requests not to. Regardless of the reasons for trial discontinuation, patients should be followed up daily for safety for a minimum of three days (five elimination half-lives) from the last dose of IMP.

12.11. End of trial definition

The end of the trial (EOT) is defined as the last patient having completed their 180-day follow-up. The CI is delegated the responsibility of submitting the EOT notification to REC and MHRA once reviewed by sponsor. The EOT notification must be received by REC and MHRA within 90 days of the end of the trial.

13. LABORATORIES AND SAMPLES

13.1. Central laboratories

The primary outcome will be based on serum high sensitivity troponin-T (Elecsys, Roche Diagnostics) measured in blood samples collected on the day of surgery before induction of anaesthesia and on days one, two and three after surgery. The samples will be analysed in batches in a timely manner for practical reasons. The results of the analyses will be masked from the blinded investigators. The analysis will be conducted by The Doctor's Laboratory.

13.2. Sample collection labelling and logging

All blood samples will be pseudo-anonymised. Samples collected at each participating site will be labelled with the participant's corresponding trial ID and kept in a hospital freezer at an optimal temperature for the troponin assay until collection. The samples will be routinely collected and transferred to WHRI where they will be stored prior to transfer to The Doctor's Laboratory. The full sample, collection, labelling, logging and transfer procedure will be documented in the study laboratory log. The trial coordinating team will provide sites with a SOP on sample collection, processing and storage.

13.3. Sample receipt/chain of custody/accountability

Handling of the samples upon arrival at the local and central laboratory will be documented. All samples will be logged upon receipt and the laboratory will ensure that the physical integrity of these samples have not been compromised in transit. If compromise has occurred, the trial coordinating team, as well as the Sponsor, will be informed of this. Upon receipt of samples, laboratory staff will ensure that all samples are accounted for as per the labelling.

13.4. Sample storage procedures

The samples will be stored in pseudo-anonymised form with the participant's trial ID written on the label in a local hospital freezer at an optimal temperature for the troponin assay until collection. The samples should be put in the freezer within two hours of preparation. The samples will not be destroyed if a patient withdraws from the study unless they specifically request so. If the patient requests for the samples to be destroyed the Tissue Custodian (CI), will inform the lab who will ensure the samples are destructed as per the Human Tissue Act. This will be documented in the TMF and ISF of the participating site.

13.5. Sample and data recording/reporting

Troponin-T data will be measured by the central laboratory and shared by secure electronic communication after the last patient sample has been analysed.

13.6. End of study

The samples will be stored beyond the end of the trial to be used for closely related studies in the future. After completion of any potential sub-studies the samples will be destroyed according to the Human Tissue Authority's Code of Practice.

14. TRIAL MEDICATION

14.1. Name and description of investigational medicinal product(s) (IMPs)

Ivabradine is the active IMP in this clinical trial and together with the placebo, the IMP supply will be arranged by MODEPHARMA for the entire duration of this trial. The active IMP will consist of a generic ivabradine 2.5mg film-coated tablet. To maintain blinding, high quality placebo film-coated tablets will be manufactured to provide a complete match with regards to the appearance of the ivabradine 2.5mg film-coated tablets being used. All active and placebo tablets will be packed in labelled blister packs with tamper-evident seals. Each pack will contain 18 active or placebo tablets. All blisters and packs will be labelled in accordance with Annex 13 guidelines. Further details about the active and placebo IMP can be found in the IMP dossier.

14.2. Legal status of the drug

Ivabradine is licensed for use in the UK for treatment of chronic stable angina pectoris and treatment of chronic heart failure. The trial is being carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

14.3. Summary of Product Characteristics (SmPC)

The SmPC used for this trial is Aspire Pharma Ltd 2.5mg ivabradine (see appendix D).

14.4. Drug storage and supply

Trial specific stock will be distributed to each site following the final Qualified Person (QP) release, once all regulatory and local approvals are in place. Shipments to sites are initiated by the trial management who will monitor IMP stocks at each site and subsequently initiate re-supplies.

14.5. Supplier/Manufacturer

The IMP supply will be arranged by MODEPHARMA. All IMPs are manufactured according to current GMP and QP released in the UK for clinical trial use.

14.6. How the drug should be stored

The IMP has no special storage conditions and the SmPC will be followed for any special instructions.

14.7. Details of accountability and destruction

The pharmacy clinical trials team must maintain accurate accountability records of the IMP, including, but not limited to, the number of packs received, the number of packs dispensed to which participant, batch number, expiry date, and quantity of IMP product returned by the participant.

Any unused IMP and/or empty packaging will be returned to pharmacy for accountability. This will be verified by the clinical trial monitor prior to disposal at site. Destruction of IMP must be in accordance with the site IMP destruction SOP.

14.8. Prescription of IMP/placebo/NIMP

The trial medication must only be used to treat participants in the FUNNY trial. Tablets for randomised patients should be taken from the FUNNY trial stock only. Only the PI or a person appropriately trained and assigned on the delegation log, will be allowed to prescribe the drug to the participant.

14.9. Preparation and labelling of IMP

All active and placebo tablets will be packed in labelled blister packs with tamper-evident seals. Each pack will contain 18 active or placebo tablets. All blisters and packs will be labelled in accordance with Annex 13 guidelines.

14.10. Preparation and administration of IMP

The IMP does not require any special preparation. The IMP dosage will be determined by the participant's baseline heart rate as detailed in section 11.4.

14.11. Dispensing of IMP

MODEPHARMA will arrange the supply of IMP to all participating centers. The dispensing of the IMP kit will vary at each site depending on whether the drug is stored with Pharmacy or the research team. The exact procedures at each site will be agreed with the Sponsor prior to site activation and clearly documented in the investigator site file. The drug should be kept in a dry, safe place according to the SmPC (appendix D). Trial-specific working practices will be supplied to the centre pharmacist in the Pharmacy Manual. The drug will be only be dispensed

by staff that are trained in the trial procedures and are delegated to do so. Each member of staff who dispenses the IMP signs the local/pharmacy dispensing log to document appropriate IMP tracking.

14.12. Assessment of compliance

The tablets will be taken by the patient in the presence of a member of the direct clinical care team who will ensure that all required tables are swallowed. The number of tablets administered and the time of administration will be recorded on the drug chart. If an incorrect number of tablets are administered or a dose is missed, a protocol deviation form should be completed.

14.13. Arrangements for post-trial access to IMP and care

At the end of the trial, either planned or prematurely, MODEPHARMA will no longer provide ivabradine to participating sites.

14.14. Concomitant medication

During the trial all anaesthesia related interventions needed for analgesia or hypnosis are allowed and management of perioperative complications (e.g. hypotension, hypoxemia, bleeding) will be left to the discretion of the clinicians in charge of the patient.

The following concomitant medications are not permitted while taking part in the trial: CYP3A4 inhibitors and CYP3A4 inducers; grapefruit products and St John's Wort; QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone) and non cardiovascular QT prolonging medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

Full details of interaction with other medicinal products and other forms of interaction can be found listed in appendix D (SmPC section 28.4.4.5). A full review will be done preoperatively prior to informed consent.

15. PHARMACOVIGILANCE

15.1. Safety outcomes

Safety data will be reported based on reviewing the patients' medical records and discussion with the patient. Since ivabradine is already licenced and well-studied in the target age group, only certain safety events as outlined below will be collected as part of the trial procedures. Due to the specificity of ivabradine on the sinoatrial node only events specific to the drug action

are collected. It is expected that patients undergoing non-cardiac surgery may often suffer from medical complications, up to and including death. As a result a large number of participants will experience complications following surgery, which are completely unrelated to the trial intervention. These surgical complications will be collected separately as part of outcome data.

Pharmacovigilance reporting will start from the completion of informed consent and stop no earlier than on day 30, the last day of talking to the patient. This will require either (1) review of the participant's medical notes if in hospital or (2) a telephone call with the participant. In the event the research team are unable to speak with the participant, their GP will be contacted.

For this study the following events will be reported and assessed accordingly:

- **pre-defined cardiovascular events (listed below)**
- **events possibly or definitely related to the trial procedures**
- **all SAEs, except those listed in appendix E, unless the investigator believes that the IMP caused the event**

The events listed below are frequently observed in high-risk surgical patients in normal practice, but also serve as safety outcome measures for the trial:

1. Bradycardia <45bpm requiring rescue therapy according to local hospital guidelines and/or pacing detected as part of routine clinical care within the first six postoperative days
2. Atrial fibrillation detected as part of routine clinical care within the first six postoperative days
3. Tachycardia >100bpm requiring treatment as recorded clinically within the first six postoperative days
4. Hypotension (MAP <60mmHg) detected as part of routine clinical care requiring pressor infusion within the first six days postoperative days
5. Phosphenes (the experience of seeing light without light actually entering the eye) within the first six postoperative days

If participants require rescue treatment for bradycardia according to local hospital policy, the next scheduled dose will be omitted. This will be documented in the eCRF. Intraoperative bradycardia occurring as a result of surgical manipulation is not uncommon. If an intraoperative

bradycardia <45bpm requires rescue therapy according to local hospital guidelines but is clearly attributable in the view of the local PI to surgical manipulation, further dosing is permitted. Any scheduled doses after a bradycardia event must be discussed with the PI.

15.2. General Definitions

Term	Definition
Adverse Event (AE)	An untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical event Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI)

15.3. Site investigators assessment

The PI is responsible for the care of the participant, or in his/her absence an authorised doctor within the research team is responsible for assessment of any event for:

Seriousness

Assessing whether the event is serious.

Causality

Assessing the causality of all AEs/SAEs/SARs in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

Expectedness

Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

Severity

Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

Due to the blinded nature of the trial, seriousness, causality and expectedness is assessed with the assumption that the participant is in the ivabradine arm.

15.4. Reference safety information

The Aspire Pharma Ltd 2.5mg ivabradine SmPC (section 28.4.4.8 in appendix D), will be used as the RSI.

15.5. Notification and reporting AEs, ARs, SAEs, SARs and SUSARs

All adverse events (AEs) are recorded on the eCRF, AE log in the ISF, recorded in the participant’s medical notes (electronic or paper as appropriate) by the PI and followed-up by the research team until the event resolves. All SAEs/SARs and SUSARs will additionally need

to be reported to the Sponsor (as per IMP supply agreement) within 24 hours of the PI or co-investigators becoming aware of the event. If an SAR has been categorised as unexpected by the trial coordinators, they will un-blind themselves via the online database without breaking the site's or CI's blinded status. If the SAR is a SUSAR it will then be reported to the competent authority and REC.

15.6. Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of SAEs and SUSARs to the CI. The CI as Sponsor medical assessor will review the event blinded for all possible IMPs/combinations within 72 hours of receipt. This review will encompass seriousness, relatedness and expectedness. Day one for all SAEs/SARs and SUSARs is when any member of the study team identifies the SAE. It is expected that the CI will achieve oversight of IMP safety profile through trial committees as per section 25. It is noted that the CI can upgrade an event to 'related' or 'unexpected' but cannot downgrade the PI assessment of an event to 'unrelated' or 'expected'. If there is disagreement between CI and PI assessment, it is the CI's responsibility to liaise with the site PI before CI's final decision. The CI and PI assessment can differ.

15.7. Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the regulatory authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed change with the Sponsor. The CI has an obligation to inform both the regulatory authority and REC in writing within three days, in the form of a substantial amendment. The Sponsor must be sent a copy of the correspondence with regards to this matter.

15.8 Pregnancy

Women of childbearing potential are excluded from participating in the trial. In the unlikely event that a trial participant is found to be pregnant while on the trial, the PI will notify the CI and sponsor within 24 hours of becoming aware of the event using the Sponsor's Pregnancy Reporting form. The sponsor will obtain independent advice from a suitable medical expert. The participant will be withdrawn from the trial immediately but will be followed-up until completion of the pregnancy. Significant updates should be notified to the CI and sponsor by updating the pregnancy report form.

16. ANNUAL REPORTING

16.1. Development safety update report (DSUR)

The DSUR will be written by the CI (using Sponsor template) and submitted to the Sponsor for review prior to submission to the regulatory authority. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "notice of acceptance letter" from the MHRA. As delegated Sponsor medical assessor the CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. REC will be sent a copy of the DSUR.

16.2. Annual progress report (APR)

The APR will be written by the CI (using HRA template) and submitted to the Sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

17. STATISTICAL AND DATA ANALYSIS

17.1. Sample size calculation

The total sample size is 350 patients with 175 participants assigned randomly to each arm. This will include a dropout rate of 1%. This sample size is based on VISION-UK data which showed that morbidity associated with troponin elevation (≥15ng L) in the first 24 hours after surgery is experienced by 59% of patients.[28] By contrast, 41% of patients without any troponin elevation sustained postoperative morbidity, representing a 31% lower relative risk of morbidity after surgery compared to patients who sustained myocardial injury defined by elevation in troponin. Assuming a conservative relative risk reduction of 25%, 173 patients will be required in each arm if ivabradine reduces the incidence of troponin-associated morbidity from 59% (placebo) to 44% (α=0.05; 1-β=0.8).

17.2. Statistical analysis plan

A full statistical analysis plan will be developed prior to any interim or final analysis. During the recruitment period the statistician will perform a safety analysis if specifically requested by the DMEC. This will be outlined accordingly in the DMEC charter.

17.3. Summary of baseline data and flow of patients

Baseline characteristics and clinical data for patients randomised to ivabradine and placebo will be summarised but not subjected to statistical testing. Numbers (%) for categorical variables and means (SD) or medians (IQR) for continuous variables as appropriate will be provided separately for each group. All participating sites have been asked to keep a log of

eligible patients not recruited to the trial. Reasons for non-participation will be categorised and summarised. Participation in the trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram

17.4. Primary outcome analysis

All analyses will be conducted according to the intention to treat principle, meaning that all randomised participants with a recorded outcome will be included in the analysis, and analysed according to the treatment to which they were randomised. The primary outcome will be analysed using a logistic regression model. The model will be adjusted for minimisation variables (trial centre and planned surgical procedure (surgery involving the gut, all other surgery)). The model will also be adjusted for pre-specified baseline covariates: age, gender (M/F) and the medical risk factor (see appendix A). All covariates will be entered into the model as fixed factors. Age will be included as a continuous variable, assuming a linear association with the outcome. The magnitude of the treatment effect will be reported as an adjusted odds ratio with a 95% confidence interval. Significance will be set at $p<0.05$.

Similar analyses of secondary outcomes will be undertaken by intention to treat principle, according to the treatment to which they were randomised. See the Statistical Analysis Plan for further information.

18. DATA HANDLING & RECORD KEEPING

18.1. Confidentiality

The PI has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and REC Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act 2018 and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined by the Sponsor. The CI and the study team will adhere to these parameters to ensure that the participant's identity is protected at every stage of their participation within the study. Patients will be anonymised with regards to any publications relating to this study.

18.2. Data custodian details

The CI is the 'Data Custodian' and maintains access to the data.

18.3. Pseudo-anonymisation

The patient's initials will be used as a means of pseudo-anonymising parameters. This information will be kept on a screening log, which will be updated accordingly throughout the study. Once the patient has completed screening procedures and is randomised, they will be allocated a trial ID that will be used to refer to the patient for the remainder of the study.

18.4. Transferring/transporting data

No patient identifiable details will be transferred outside the participating hospital nor shared with the study Sponsor. Only anonymised data will be uploaded onto the study database.

18.5. Case report form

On data collection times illustrated in section 12.7.2, research staff will be responsible for the completion of the eCRF throughout the life cycle of the study. The eCRF will be custom designed by QMUL and will be hosted on a secure server. The main data points that are collected can be seen in section 12.8. Sites will be provided with a paper data collection tool that matches the eCRF however it is not compulsory to complete this. The eCRF will count as source data for patient reported outcomes collected during the 30-day follow-up. Patients' medical notes will act as source for the rest of the data, including safety data (AEs, SAEs, and SUSARs). It is expected that the exact source data list will vary by site.

18.6. Data handling and record keeping

Data can be transcribed onto the data collection tool prior to entry on to the secure data entry web portal but can also be entered directly onto the eCRF. Submitted data will be reviewed for completeness and consistency by authorised users within the trial coordinating team. Submitted data will be stored securely against unauthorised manipulation and accidental loss. Only authorised users at site, or at QMUL will have access. Desktop security is maintained through usernames and passwords. Data back-up procedures are in place and a full audit trail will be kept. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK).

18.7. Access to data, source data and documents

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

18.8. Archiving

During the course of research, the CI has full responsibility of all study records which must be kept in secure conditions at all times. When the trial is complete, it is a requirement of the UK Policy Framework and Trust Policy that the records are kept for a further 25 years. Archiving will be authorised by the Sponsor following submission of the end of study report. The Sponsor is responsible for maintaining and archiving the study TMF. The study database will be stored according to the Sponsor's policies. Anonymised electronic data sets will be stored indefinitely.

The sites are responsible for maintaining and archiving all local records including the ISF and eCRFs. These records should be archived together once authorisation has been given by the Sponsor. It is the responsibility of the PI to ensure a full set of records is collated and documented. In addition, source documentation should be retained, as per local policy, for the duration of the archiving period. Destruction of essential documents will require authorisation from the Sponsor.

19. MONITORING, AUDIT AND INSPECTION

The Sponsor will have oversight of the trial conduct at each site. The trial coordinating team will take day-to-day responsibility for ensuring compliance with the requirements of GCP in terms of quality control and quality assurance of the data collected as well as safety reporting. The Trial Management Group (TMG) will communicate closely with individual sites and the Sponsor's representatives to ensure these processes are effective.

19.1. Monitoring

A trial monitoring plan will be developed and agreed by the Sponsor and CI based on the Sponsor's trial risk assessment.

19.2. Auditing

Sponsor retains the right to audit any trial, trial site or central facility. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable.

19.3. Notification of serious breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The site PI is responsible for reporting any serious breaches to the Sponsor within 24 hours. The CI is responsible for reporting any serious breaches to the Sponsor within 24 hours. The Sponsor will work with the CI to investigate any potential breach and notify and report to the competent authority (as applicable) within 7 working days of becoming aware of the serious breach.

20. COMPLIANCE

The CI will ensure that the trial is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, General Data Protection Regulations, current UK Policy Framework, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

20.1. Non-compliance

Non-compliances may be captured from a variety of different sources including monitoring visits, eCRFs, communications and updates. The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The CI and the trial coordinating team should assess the non-compliances and action a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the Sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the Sponsor within 24 hours of the trial coordinating team becoming aware. Where applicable corrective and preventative actions (CAPA) should be assigned. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, including an on-site audit. Deviations from the protocol which are found to frequently recur are not acceptable. This will require immediate action and could potentially be classified as a serious breach. Protocol deviations must be documented on the supplementary form in the eCRF.

21. ETHICAL AND REGULATORY CONSIDERATIONS

The trial will not commence until a Clinical Trial Authorisation (CTA) from the relevant national Competent Authority and a full approval from the National ethical committee has been obtained. Before any site can enrol participants into the trial, Site organisational and departmental approval must be obtained as relevant to national requirements.

21.1. Amendments

Substantial and non-substantial amendments will be made by the CI and the trial coordinating team. Prior to submission of all amendment a permission from the Sponsor will be sought beforehand. After the Sponsor's approval the documents will submitted to the National ethical committees and regulatory competent authorities according to the predefined national process. Decisions on whether an amendment constitutes as a minor or substantial amendment lies with the Sponsor. Amendments will also be notified to Site research oversight departments of the participating sites via email to be assessed and approved as per local requirements.

22. PEER REVIEW

This protocol is based on the competitively awarded NIHR Advanced Fellowship grant to Professor Ackland, which was peer reviewed by nine experts, plus a 15-strong interview panel. Since securing the award, the protocol has been further reviewed during the application process.

23. PUBLIC AND PARTICIPANT INVOLVEMENT (PPI)

This protocol is based on the NIHR Advanced Fellowship grant and meets the NIHR PPI requirements prior to the award. The protocol has since also been reviewed by the PPI member appointed to advise the FUNNY study group.

24. INDEMNITY

QMUL will act as trial Sponsor and provide no fault insurance.

25. TRIAL COMMITTEES

25.1. Trial management group (TMG)

Day-to-day management of the trial will be co-ordinated by the trial coordinating team consisting of the CI and their support staff (e.g. trial coordinator and statistician).

25.2. Trial steering committee (TSC)

The TSC will oversee the trial and will consist of several independent clinicians and trialists, lay representation, co-investigators and an independent chair. Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- major decisions such as a need to change the protocol for any reason
- monitoring and supervising the progress of the trial

- reviewing relevant information from other sources
- considering recommendations from the DMEC
- informing and advising on all aspects of the trial

All members of the TSC will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.

25.3. Data monitoring and ethics committee (DMEC)

The DMEC is independent of the trial coordinating team and comprises of a minimum of two clinicians with experience in undertaking clinical studies and a statistician. The DMEC functions primarily to periodically review overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The committee will also review relevant new external evidence and monitor the overall conduct of the study. The committee will agree conduct and remit, which will include the early termination process. The study will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. Generally, the CI identifies any relevant external evidence and passes this to the DMEC Chair for review by the DMEC. The DMEC will provide recommendations about stopping, modifying or continuing the study to the TSC. The DMEC may also make recommendations regarding selection, recruitment, or retention of participants, their management, protocol adherence and retention of participants, and procedures for data management and quality control. The TSC will be responsible for promptly reviewing the DMEC recommendations, to decide whether to continue or terminate the study, and to determine whether amendments to the protocol or changes in study conduct are required.

26. PUBLICATION AND DISSEMINATION POLICY

This is an investigator-led study sponsored by the CI's substantive employer, QMUL. The data collected will not be used to license and/or register any pharmaceuticals. Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal. At least one of the lay members will contribute to the dissemination of protocol and final manuscripts. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the design, committee membership, accrual of eligible patients and statistical analysis. All authors will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. The funders, contributing centres (and participating investigators) will be acknowledged in the final manuscript. No investigator may present data from his/her centre separately from the rest of

the study results unless approved by the TSC and the Sponsor. All members of the trial committees will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial. The full study report will be submitted to the NIHR and will also be made accessible via EudraCT and ISRCTN.

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28. APPENDICES

28.1. Appendix A: Medical risk factors for inclusion, where ≥1 need to be fulfilled

- Coronary artery disease
- Diabetes mellitus requiring oral hypoglycemic agent and/or insulin
- Congestive heart failure
- Cerebrovascular accident
- Chronic kidney disease stage 3-5 (eGFR <59ml/min/1.73m^2)
- Peripheral arterial disease
- History of hypertension (requiring anti-hypertensive drug)

28.2. Appendix B: Postoperative morbidity survey (POMS)

	Has the patient had, or developed, in the last 24h:	**YES**	**NO**
Pulmonary	A new requirement for oxygen	☐	☐
	A new requirement for respiratory support?	☐	☐
Infections	Is the patient currently on antibiotics	☐	☐
	Has the patient had a temperature of ≥38°C?	☐	☐
Renal	Presence of oliguria (<500 mL/day)	☐	☐
	Increased serum creatinine (>30% from preoperative level)	☐	☐
	Urinary catheter *in situ* (for a nonsurgical reason)	☐	☐
Gastrointestinal	Unable to tolerate enteral diet (oral or tube feed) for any reason?	☐	☐
	Is the patient experiencing nausea, vomiting, or abdominal distention (including use of anti-emetic)?	☐	☐
Cardiovascular	Has the patient undergone diagnostic tests or therapy for any of the following:		
	New myocardial infarction	☐	☐
	New myocardial ischaemia	☐	☐
	Hypotension (requiring drug therapy or fluid therapy >200 mL/h)?	☐	☐
	Atrial or ventricular arrhythmias?	☐	☐
	Cardiogenic pulmonary oedema	☐	☐
	De novo full anticoagulation	☐	☐
Neurological	Confusion/delirium	☐	☐
	Coma	☐	☐
	Focal neurological deficit	☐	☐
Wound complications	Wound dehiscence requiring surgical exploration	☐	☐
	Drainage of pus from the operation wound with/without isolation of organisms?	☐	☐
Haematological	Red packed cells	☐	☐
	Blood products (e.g platelets/FFP/cryoprecipitate)	☐	☐
Pain	Wound pain significant enough to require parenteral opioids	☐	☐
	Wound pain significant enough to require regional analgesia	☐	☐
Mobility	Is the patient bedbound	☐	☐
	Does the patient mobilise unaided	☐	☐

28.3. Appendix C: Clavien-Dindo grading and complication definitions

Clavien-Dindo scale grading:

I. Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention. Anti-emetics, anti-pyretics, diruetics, electrolytes or physiotherapy are not considered a deviation from the normal postoperative course.
II. Requires pharmacological treatment with drugs (including blood transfusion or total parenteral nutrition) other than those excluded from grade I.
III. Requires surgical, endoscopic or radiological intervention.
IV. Life-threatening complication requiring critical care admission
V. Death

Definitions:

Cardiovascular events

Myocardial infarction

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:

- Symptoms of ischemia
- New or presumed new significant ST-segment or T-wave ECG changes or new left bundle branch block
- Development of pathological Q-waves on ECG
- Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intra-coronary thrombus at angiography or autopsy

Arrhythmia

Arrhythmia is defined as electrocardiograph (ECG) evidence of cardiac rhythm disturbance.

Cardiogenic pulmonary oedema

Cardiogenic pulmonary oedema is defined as evidence of fluid accumulation in the alveoli due to poor cardiac function.

Hypertension

Systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 100 mmHg.

Hypotension

MAP <60mmHg or systolic BP is <90mmHg, detected as part of routine clinical care requiring pressor infusion.

Bradycardia

<45bpm requiring rescue therapy according to local hospital guidelines and/or pacing detected as part of routine clinical care.

Refractory bradycardia

Bradycardia unresponsive to pharmacological therapy.

Cardiac arrest with successful resuscitation:

Clinical diagnosis of cardiac arrest followed by return of spontaneous circulation for at least one hour.

Respiratory events

Pneumonia

This is defined as two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

- new or progressive and persistent infiltrates
- consolidation
- cavitation

And at least one of the following:

- fever (>38°C) with no other recognized cause
- leucopenia (<4 x 10^9 L) or leucocytosis (>12 x 10^9 L)
- for adults >70 years old, altered mental status with no other recognised cause

And at least two of the following:

- new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
- new onset or worsening cough, or dyspnoea, or tachypnoea

- rales or bronchial breath sounds
- worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand)

Pneumothorax

Air in the pleural cavity with no visceral bed surrounding the visceral pleura. Usually results from damage to the pleural membranes or lung tissue.

Bronchospasm

Newly detected expiratory wheeze treated with bronchodilators.

Aspiration pneumonitis

Acute lung injury after the inhalation of gastric contents.

Acute Lung Injury:

PaO_2: FiO_2 less than 300 mmHg

Acute respiratory distress syndrome (ARDS):

a) Develops within one week of surgery AND
b) chest radiograph or computed tomography scan demonstrating bilateral opacities not fully explained by effusions, lobar Lung collapse or nodules AND
c) respiratory failure not fully explained by cardiac failure or fluid overload AND
d) oxygenation meets one of the following criteria (note severity still graded according to Clavien-Dindo system):
   - Mild: PaO_2: FiO_2 between 200 and 300 mmHg with PEEP or CPAP ≥5 cmH2Oc
   - Moderate: PaO_2: FiO_2 between 100 and 200 mmHg with PEEP ≥5 cmH2O
   - Severe: PaO_2: FiO_2 ≤100 mmHg with PEEP ≥5 cmH2O

Infective complications

Surgical site infection (SSI) (superficial)

a) Involves only skin and sub-cutaneous tissue of the incision AND
b) the patient has at least one of the following:
   - purulent drainage from the superficial incision
   - organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision

- at least one of the following symptoms or signs of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.
- diagnosis of an incisional surgical site infection by a surgeon or attending physician.

Surgical site infection (deep)

a) Involves deep soft tissues (e.g. fascial and muscle layers) of the incision AND
b) the patient has at least one of the following:
   - purulent drainage from the deep incision but not from the organ/space component of the surgical site
   - a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured when the patient has at least one of the following symptoms or signs: fever (>38^{o}C), or localized pain or tenderness. A culture-negative finding does not meet this criterion.
   - an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathologic or radiologic examination.
   - diagnosis of an incisional surgical site infection by a surgeon or attending physician.

Surgical site infection (organ space)

An infection at the surgical incision site involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and the patient has at least one of the following:

- purulent drainage from a drain that is placed through a stab wound into the organ/space.
- organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
- an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- diagnosis of an organ/space surgical site infection by a surgeon or attending physician.

Urinary tract infection

A positive urine culture of ≥10^5 colony forming units/mL with no more than two species of micro-organisms with at least one of the following symptoms or signs:

- fever (>38°C)
- urgency
- frequency
- dysuria
- supra-pubic tenderness
- costo-vertebral angle pain or tenderness with no other recognised cause, identified within a 24-hour period.

Alternatively, the patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation, or during a histopathologic examination with one of the following:

- purulent drainage from affected site
- radiographic evidence of infection
- physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space
- physician institutes antibiotic therapy for an infection of the kidney, ureter, bladder, urethra, or surrounding tissues

Infection, source uncertain

An infection which is considered likely to be one of the following but cannot be differentiated because clinical information suggests more than one possible site: superficial SSI, or deep SSI, or organ space SSI, or pneumonia, or urinary tract infection, or laboratory confirmed blood stream infection. There must be a strong clinical suspicion of infection meeting two or more of the following criteria:

- core temperature <36°C or >38°
- white cell count >12 x 10^9 L or <4 x 10^9 L
- respiratory rate >20 breaths per minute or $PaCO_2$ <35 mmHg
- pulse rate >90 beats per minute

Laboratory confirmed bloodstream infection

An infection which meets at least one of the following criteria but is not related to infection at another site:

- Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site
- Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following:
  - common skin contaminant cultured from two or more blood cultures drawn on separate occasions
  - common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes antimicrobial therapy
  - positive blood antigen test

Other defined postoperative complications

Pulmonary embolism

A new blood clot or thrombus within the pulmonary arterial system. Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery.

Stroke

An embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).

Acute psychosis or delirium

Acute episode of severe confusion or personality change, which may result in hallucinations or delusional beliefs in the absence of a pre-existing diagnosis, which may account for the clinical symptoms and signs.

Bowel infarction

Clinical diagnosis demonstrated at laparotomy.

Anastomotic leak

Demonstrated at laparotomy or by contrast enhanced radiograph or CT scan.

Perforation of viscus

Clinical diagnosis demonstrated at laparotomy or confirmed by contrast enhanced radiograph or CT scan. For example perforated bowel, gall bladder etc.

Gastrointestinal bleed

Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz, in practice from the oesophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel and colon.

Other postoperative haemorrhage (not gastrointestinal bleed)

Blood loss within 72 hours after the start of surgery, which would normally result in transfusion of blood.

Acute kidney injury: Please see KDIGO staging criteria below:

Staging	Serum Creatinine	Urine output
1	1.5-1.9 times baseline OR ≥ 0.3mg/dl (≥26.5µmol L) increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0mg/dl (≥353.6 mcmol L) OR Initiation of renal replacement therapy OR In patients < 18 years, decrease in eGFR to < 35ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Other definitions:

Level of care after surgery

The level of care should be defined according to the care the patient received rather than the location. For example, a patient receiving level 2 care in a level 3 area should be recorded as receiving level 2 care.

i) Critical care level three: includes advanced organ support e.g. invasive ventilation, renal replacement therapy.
ii) Critical care level two: may include advanced cardiorespiratory monitoring (e.g. invasive arterial / central venous monitoring) and basic organ support (e.g. non-invasive ventilation, inotropic/vasoactive drug administration).
iii) Post-anaesthetic care unit/recovery: care within a designated area for the patients in the immediate recovery from anaesthesia. May deliver care at levels 1 to 3.
iv) Surgical ward (level 0/1): normal ward care without level 2 or 3 capabilities.

Elective surgery

Surgical procedure planned or booked in advance of routine admission to hospital

Urgent surgery

Acute onset or deterioration of conditions that threaten life, limb or organ survival; fixation of fractures; relief of distressing symptoms.

28.4. Appendix D: SmPC for Aspire Pharma Ltd 2.5mg ivabradine

28.7.1. Name of the medicinal product

Ivabradine Aspire 2.5 mg film-coated tablets

28.7.2. Qualitative and quantitative composition

One film-coated tablet contains 2.5 mg ivabradine (equivalent to 2.695 mg ivabradine as hydrochloride).

Excipient with known effect: 26.35.mg lactose monohydrate

For the full list of excipients, see section 28.4.6.1.

28.7.3. Pharmaceutical form

Film-coated tablet.

Yellow, round, biconvex film-coated tablet 5 mm in diameter and 2.2 ± 0.2 mm in thickness.

28.7.4. Clinical particulars

28.4.4.1 Therapeutic indications

Symptomatic treatment of chronic stable angina pectoris.

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated:

- in adults unable to tolerate or with a contraindication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Treatment of chronic heart failure

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard

therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated (see section 28.4.5.1).

28.4.4.2 Posology and method of administration

Posology

For the different doses, film-coated tablets containing 2.5 mg, 5 mg and 7.5 mg ivabradine are available.

Symptomatic treatment of chronic stable angina pectoris

It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring.

The starting dose of ivabradine should not exceed 5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.

If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of ivabradine should be discontinued.

In addition, discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.

If, during treatment, heart rate decreases below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the lowest dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). After dose reduction, heart rate should be monitored (see section 28.4.4.4). Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

Treatment of chronic heart failure

The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as

dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 28.4.4.).

Special population

Elderly people

In patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily) before up-titration if necessary.

Renal impairment

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see section 28.4.5.2).

No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contraindicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated (see sections 28.4.4.3 and 28.4.5.2).

Paediatric population

The safety and efficacy of ivabradine in children aged below 18 years have not been established.
Currently available data for the treatment of chronic heart failure are described in sections 28.4.5.1 and 28.4.5.2 but no recommendation on a posology can be made.

Available data are described in sections 28.4.5.1 and 28.4.5.2 but no recommendation on a posology can be made.

No data for symptomatic treatment of chronic stable angina pectoris are available.

Method of administration

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals (see section 28.4.5.2).

28.4.4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Resting heart rate below 70 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone (see sections 28.4.4.5 and 28.4.5.2)
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties (see section 28.4.4.5)
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures (see section 28.4.4.6)

28.4.4.4 Special warnings and precautions for use

Special warnings

Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris

Ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) (see section 28.4.5.1).

Measurement of heart rate

Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart

rate before initiation of ivabradine treatment and in patients on treatment with ivabradine when titration is considered. This also applies to patients with a low heart rate, in particular when heart rate decreases below 50 bpm, or after dose reduction (see section 28.4.4.2).

Cardiac arrhythmias

Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (eg. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.

In patients treated with ivabradine the risk of developing atrial fibrillation is increased (see section 28.4.4.8). Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics. It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse). Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Use in patients with AV-block of 2nd degree

Ivabradine is not recommended in patients with AV-block of 2nd degree.

Use in patients with a low heart rate

Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minute (see section 28.4.4.3).

If, during treatment, resting heart rate decreases persistently below 50 bpm or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward or treatment discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 28.4.4.2).

Combination with calcium channel blockers

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated (see sections 28.4.4.3 and 28.4.4.5). No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium

channel blockers such as amlodipine. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established (see section 28.4.5.1).

Chronic heart failure

Heart failure must be stable before considering ivabradine treatment. Ivabradine should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population.

Stroke

The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.

Visual function

Ivabradine influences retinal function. There is no evidence of a toxic effect of long-term ivabradine on the retina (see section 28.4.5.1). Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Precautions for use

Patients with hypotension

Limited data are available in patients with mild to moderate hypotension, and ivabradine should therefore be used with caution in these patients. Ivabradine is contraindicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see section 28.4.4.3).

Atrial fibrillation - Cardiac arrhythmias

There is no evidence of risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the absence of extensive data, non urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products

The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided (see section 28.4.4.5). If the combination appears necessary, close cardiac monitoring is needed.

Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which may give rise to severe arrhythmias, in particular *Torsade de pointes.*

Hypertensive patients requiring blood pressure treatment modifications.

When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval (see section 28.4.4.8).

Excipients

Since tablets contain lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

28.4.4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Concomitant use not recommended

QT prolonging medicinal products

- Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular QT prolonging medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

The concomitant use of cardiovascular and non cardiovascular QT prolonging medicinal products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed (see section 28.4.4.4).

Concomitant use with precaution

Potassium-depleting diuretics (thiazide diuretics and loop diuretics)

Hypokalaemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalaemia and bradycardia is a predisposing factor to the onset of severe arrhythmias, especially in patients with long QT syndrome, whether congenital or substance-induced.

Pharmacokinetic interactions

Ivabradine is metabolised by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Ivabradine was shown not to influence the metabolism and plasma concentrations of other CYP3A4 substrates (mild, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Interaction studies have established that CYP3A4 inhibitors

increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia (see section 28.4.4.4).

Contraindication of concomitant use

Potent CYP3A4 inhibitors

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contraindicated (see section 28.4.4.3). The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased ivabradine mean plasma exposure by 7 to 8 fold.

Moderate CYP3A4 inhibitors

Specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicinal products is contraindicated (see section 28.4.4.3).

Concomitant use not recommended

Grapefruit juice: ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be avoided.

Concomitant use with precautions

- Moderate CYP3A4 inhibitors: the concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 70 bpm, with monitoring of heart rate.
- CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, *Hypericum perforatum* [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. The combination of ivabradine 10 mg twice daily with St John's Wort was shown to reduce ivabradine AUC by half. The intake of St John's Wort should be restricted during the treatment with ivabradine.

Other concomitant use

Specific drug-drug interaction studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin),

dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.

In pivotal phase III clinical trials the following medicinal products were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet medicinal products.

Paediatric population

Interaction studies have only been performed in adults.

28.4.4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 28.4.4.3).

Pregnancy

There are no or limited amount of data from the use of ivabradine in pregnant women.
Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects (see section 28.4.5.3). The potential risk for humans is unknown. Therefore, ivabradine is contraindicated during pregnancy (see section 28.4.4.3).

Breast-feeding

Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contraindicated during breast-feeding (see section 28.4.4.3).

Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child.

Fertility

Studies in rats have shown no effect on fertility in males and females (see section 28.4.5.3).

28.4.4.7 Effects on ability to drive and use machines

A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, in post-marketing experience, cases of impaired driving ability due to

visual symptoms have been reported. Ivabradine may cause transient luminous phenomena consisting mainly of phosphenes (see section28.4.4.8). The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night. Ivabradine has no influence on the ability to use machines.

28.4.4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) (14.5%) and bradycardia (3.3%). They are dose dependent and related to the pharmacological effect of the medicinal product.

Tabulated list of adverse reactions

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)
	Common	Blurred vision
	Uncommon*	Diplopia
		Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles

		Atrial fibrillation
	Uncommon	Palpitations, supraventricular extrasystoles, ECG prolonged QT interval
	Very rare	AV 2nd degree block, AV 3rd degree block
		Sick sinus syndrome
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
		Constipation
		Diarrhoea
		Abdominal pain*
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
		Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
Renal and urinary disorders	Uncommon	Elevated creatinine in blood
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

Description of selected adverse reactions

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), coloured bright lights, or multiple image

(retinal persistency). The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients 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.

In the SIGNIFY study atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group. In a pooled analysis of all the Phase II/III double blind controlled clinical trials with a duration of at least 3 months including more than 40,000 patients, the incidence of atrial fibrillation was 4.86% in ivabradine treated patients compared to 4.08% in controls, corresponding to a hazard ratio of 1.26, 95% CI [1.15-1.39].

In the SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store).

28.4.4.9 Overdose

Symptoms

Overdose may lead to severe and prolonged bradycardia (see section 28.4.4.8).

Management

Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

28.7.5. Pharmacological properties

28.4.5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations, ATC code: C01EB17.

Mechanism of action

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field (see section 28.4.4.8).

Pharmacodynamic effects

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm (see section 28.4.4.8).

At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

- in clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
- in patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

Clinical efficacy and safety

The antianginal and anti-ischaemic efficacy of ivabradine was studied in five double-blind randomised trials (three versus placebo, and one each versus atenolol and amlodipine). These

trials included a total of 4,111 patients with chronic stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit over 5 mg twice daily was established in a reference-controlled study versus atenolol: total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. In this study, the antianginal and anti-ischaemic benefits of ivabradine were confirmed in patients aged 65 years or more. The efficacy of 5 and 7.5 mg twice daily was consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1mm ST segment depression) and was associated with a decrease of about 70% in the rate of angina attacks. The twice-daily dosing regimen of ivabradine gave uniform efficacy over 24 hours.

In a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. showed additional efficacy on all ETT parameters at the trough of drug activity (12 hours after oral intake).

In a 725-patients randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine 10 mg o.d. at the trough of drug activity (12 hours after oral intake) while an additional efficacy was shown at peak (3-4 hours after oral intake).

In a 1277-patients randomised placebo-controlled study, ivabradine demonstrated a statistically significant additional efficacy on response to treatment (defined as a decrease of at least 3 angina attacks per week and/or an increase in the time to 1 mm ST segment depression of at least 60 s during a treadmill ETT) on top of amlodipine 5 mg o.d. or nifedipine GITS 30 mg o.d. at the trough of drug activity (12 hours after oral ivabradine intake) over a 6-week treatment period (OR = 1.3, 95% CI [1.0–1.7]; p=0.012).

Ivabradine did not show additional efficacy on secondary endpoints of ETT parameters at the trough of drug activity while an additional efficacy was shown at peak (3-4 hours after oral ivabradine intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The antianginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure

product (heart rate x systolic blood pressure) at rest and during exercise. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year (n = 713). No influence on glucose or lipid metabolism was observed.

The antianginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients (n = 457) with a similar safety profile as compared to the overall population.

A large outcome study, BEAUTIFUL, was performed in 10917 patients with coronary artery disease and left ventricular dysfunction (LVEF <40%) on top of optimal background therapy with 86.9% of patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalisation for acute MI or hospitalisation for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine:placebo 1.00, p=0.945).

In a post-hoc subgroup of patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalisation for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05).

A large outcome study, SIGNIFY, was performed in 19102 patients with coronary artery disease and without clinical heart failure (LVEF > 40%), on top of optimal background therapy. A therapeutic scheme higher than the approved posology was used (starting dose 7.5 mg b.i.d. (5 mg b.i.d, if age ≥ 75 years) and titration up to 10 mg b.i.d). The main efficacy criterion was the composite of cardiovascular death or non-fatal MI. The study showed no difference in the rate of the primary composite endpoint (PCE) in the ivabradine group by comparison to the placebo group (relative risk ivabradine/placebo 1.08, p=0.197). Bradycardia was reported by 17.9 % of patients in the ivabradine group (2.1% in the placebo group). Verapamil, diltiazem or strong CYP 3A4 inhibitors were received by 7.1% of patients during the study.

A small statistically significant increase in the PCE was observed in a pre-specified subgroup of patients with angina patients in CCS class II or higher at baseline (n=12049) (annual rates 3.4% versus 2.9%, relative risk ivabradine/placebo 1.18, p=0.018), but not in the subgroup of the overall angina population in CCS class ≥ I (n=14286) (relative risk ivabradine/placebo 1.11, p=0.110).

The higher than approved dose used in the study did not fully explain these findings.

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6505 adult patients with stable chronic CHF (for ≥ 4

weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF ≤ 35%) and a resting heart rate ≥ 70 bpm.

Patients received standard care including beta-blockers (89 %), ACE inhibitors and/or angiotensin II antagonists (91 %), diuretics (83 %), and anti-aldosterone agents (60 %). In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95%CI [0.75;0.90] – p<0.0001) apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are mainly driven by the heart failure endpoints, hospitalisation for worsening heart failure (absolute risk reduced by 4.7 %) and deaths from heart failure (absolute risk reduced by 1.1 %).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

	Ivabradine (N=3241) n (%)	Placebo (N=3264) n (%)	Hazard ratio [95% CI]	p-value
Primary composite endpoint	793 (24.47)	937 (28.71)	0.82 [0.75; 0.90]	<0.0001
Components of the composite: - CV death - Hospitalisation for worsening HF	 449 (13.85) 514 (15.86)	 491 (15.04) 672 (20.59)	 0.91 [0.80; 1.03] 0.74 [0.66; 0.83]	 0.128 <0.0001
Other secondary endpoints: - All cause death - Death from HF - Hospitalisation for any cause - Hospitalisation for CV reason	 503 (15.52) 113 (3.49) 1231 (37.98) 977 (30.15)	 552 (16.91) 151 (4.63) 1356 (41.54) 1122 (34.38)	 0.90 [0.80; 1.02] 0.74 [0.58; 0.94] 0.89 [0.82; 0.96] 0.85 [0.78; 0.92]	 0.092 0.014 0.003 0.0002

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

In the subgroup of patients with HR ≥ 75 bpm (n=4150), a greater reduction was observed in the primary composite endpoint of 24 % (hazard ratio: 0.76, 95%CI [0.68;0.85] – p<0.0001) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95%CI [0.72;0.96] – p=0.0109) and CV death (hazard ratio: 0.83, 95%CI [0.71;0.97] – p=0.0166). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.85, 95%CI [0.76;0.94]).

In the subgroup of patients with HR ≥ 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95%CI [0.74;1.28]) and other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.53]).

There was a significant improvement in NYHA class at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo (p=0.001).

In a 97-patient randomised placebo-controlled study, the data collected during specific ophthalmologic investigations, aiming at documenting the function of the cone and rod systems and the ascending visual pathway (i.e. electroretinogram, static and kinetic visual fields, colour vision, visual acuity), in patients treated with ivabradine for chronic stable angina pectoris over 3 years, did not show any retinal toxicity.

Paediatric population

A randomised, double blind, placebo controlled study was performed in 116 paediatric patients (17 aged [6-12] months, 36 aged [1-3] years and 63 aged [3-18] years) with CHF and dilated cardiomyopathy (DCM) on top of optimal background treatment. 74 received ivabradine (ratio 2:1).

The starting dose was 0.02 mg/kg bid in age-subset [6-12] months, 0.05 mg/kg bid in [1-3] years and [3-18] years <40 kg, and 2.5 mg bid in [3-18] years and ≥ 40 kg. The dose was adapted depending on the therapeutic response with maximum doses of 0.2 mg/kg bid, 0.3 mg/kg bid and 15 mg bid respectively. In this study, ivabradine was administered as oral liquid formulation or tablet twice daily. The absence of pharmacokinetic difference between the 2

formulations was shown in an open-label randomised two-period cross-over study in 24 adult healthy volunteers.

A 20% heart rate reduction, without bradycardia, was achieved by 69.9% of patients in the ivabradine group versus 12.2% in the placebo group during the titration period of 2 to 8 weeks (Odds Ratio: E = 17.24, 95% CI [5.91 ; 50.30]).

The mean ivabradine doses allowing to achieve a 20% HRR were 0.13 ± 0.04 mg/kg bid, 0.10 ± 0.04 mg/kg bid and 4.1 ± 2.2 mg bid in the age subsets [1-3] years, [3-18] years and <40 kg and [3-18] years and ≥ 40 kg, respectively.

Mean LVEF increased from 31.8% to 45.3% at M012 in ivabradine group versus 35.4% to 42.3% in the placebo group. There was an improvement in NYHA class in 37.7% of ivabradine patients versus 25.0% in the placebo group. These improvements were not statistically significant.

The safety profile, over one year, was similar to the one described in adult CHF patients.

The long-term effects of ivabradine on growth, puberty and general development as well as the long-term efficacy of therapy with ivabradine in childhood to reduce cardiovascular morbidity and mortality have not been studied.

The European Medicines Agency has waived the obligation to submit the results of studies with Ivabradine in all subsets of the paediatric population for the treatment of angina pectoris.

The European Medicines Agency has waived the obligation to submit the results of studies with Procoralan in children aged 0 to less than 6 months for the treatment of chronic heart failure.

28.4.5.2 Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (>10 mg/ml).

Ivabradine is the S-enantiomer with no bioconversion demonstrated *in vivo*. The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans.

Absorption and bioavailability

Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30 %. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure (see section 28.4.4.2).

Distribution

Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). The average plasma concentration is 10 ng/ml (CV=38%) at steady state.

Biotransformation

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. The metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations (see section 28.4.4.5).

Elimination

Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

Linearity/non linearity

The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg.

Special populations

- Elderly people: no pharmacokinetic differences (AUC and Cmax) have been observed between elderly (≥ 65 years) or very elderly patients (≥ 75 years) and the overall population (see section 28.4.4.2).
- Renal impairment: the impact of renal impairment (creatinine clearance from 15 to 60 ml/min) on ivabradine pharmacokinetic is minimal, in relation with the low contribution of renal clearance (about 20 %) to total elimination for both ivabradine and its main metabolite S 18982 (see section 28.4.4.2).

- Hepatic impairment: in patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (see sections 28.4.4.2 and 28.4.4.3).
- Paediatric population: The pharmacokinetic profile of ivabradine in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the pharmacokinetics described in adults when a titration scheme based on age and weight is applied.

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations and tends to reach a plateau. High exposures to ivabradine that may occur when ivabradine is given in combination with strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors (see sections 28.4.4.3, 28.4.4.4 and 28.4.4.5). The PK/PD relationship of ivabradine in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the PK/PD relationship described in adults.

28.4.5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit.

In dogs given ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function were observed but were not associated with any damage to ocular structures. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated I_h currents in the retina, which share extensive homology with the cardiac pacemaker I_f current.

Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.

Environmental Risk Assessment (ERA)

The environmental risk assessment of ivabradine has been conducted in accordance to European guidelines on ERA.
Outcomes of these evaluations support the lack of environmental risk of ivabradine and ivabradine does not pose a threat to the environment.

28.7.6. Pharmaceutical particulars

28.4.6.1 List of excipients

Core

Lactose monohydrate
Magnesium stearate
Maize starch
Maltodextrin
Silica colloidal anhydrous

Film-coating

Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Yellow iron oxide (E172)

28.4.6.2 Incompatibilities

Not applicable

28.4.6.3 Shelf life

3 years

28.4.6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

28.4.6.5 Nature and contents of container

Aluminium/Aluminium blister packed in cardboard boxes containing packs of 14, 28, 56, 84, 98, 100 or 112 film-coated tablets
Not all pack sizes may be marketed

28.4.6.6 Special precautions for disposal and other handling

No special requirements

Marketing authorisation holder

Aspire Pharma Ltd
Unit 4 Rotherbrook Court
Bedford Road
Petersfield
Hampshire
GU32 3QG
United Kingdom

Marketing authorisation number(s)

PL 35533/0080

Date of first authorisation/renewal of the authorisation

12/01/2017

Date of revision of the text

28/02/2022

28.5. Appendix E: Complications which do not require recording or reporting as an SAE unless the investigator believes that the IMP caused the event.

Pulmonary

- Oxygen requirement >21% Inspired concentration.
- Non-invasive or invasive ventilation.
- Emergency reintubation.
- Incomplete reversal form neuromuscular blockade.

Infection

- Antibiotics
- Fever
- Any clinically suspected or documented infection
- Pus from wound site
- White cell count, procalcitonin, CRP or hs-CRP >upper limit of normal

Renal

- Oliguria (<500ml day urine output)
- Creatinine rise >preoperative values
- Renal replacement therapy
- Hyper/hypokalaemia
- Hyper/hypomagnesemia

Gastrointestinal

- Nausea/vomiting
- Intolerance of enteral feed
- Ileus
- AST/ALT/bilirubin/amylase change from preoperative values
- Diarrhoea

Cardiovascular

- Myocardial ischaemia
- Myocardial infarction
- Hypotension (MAP<60mmHg) or systolic BP is <90mmHg
- Pulmonary oedema [including negative pressure pulmonary oedema]
- Arrhythmia
- Prophylactic anticoagulation
- INR/APTT/D-dimer/CK/CK-MB values above normal limits.
- Fluid administration in addition to maintenance fluid for any reason.

Neurological

- Coma
- Delirium/Confusion
- Stroke
- Transient ischaemic attack

- Syncope/Pre-syncope

Wound

- Any surgical site infection, including redness or wound dehiscence

Haematological

- Administration of Packed Red Cells, Fresh frozen plasma, cryoprecipitate or platelets.
- Haemoglobin, platelet or differential white cell count above the upper limit or below the lower limit of normal

Pain

- Analgesia delivered using regional techniques and/or parental opioids.
- Reversal of opioid overdose or suspected overdose.

Mobility

- Falls
- Requiring assistance or aided
- Bedbound