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| protocol |
| **Antiarrhythmic properties of phenytoin or dantrolene** |
| Version: 4  Date: 24/04/2019 |
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# 

# **ADMINISTRATIVE INFORMATION**

## **TITLE**

“Double blinded randomized controlled trial, 12 months, to study the efficacy of phenytoin or dantrolene in controlling arrhythmias and heart failure symptoms”

## **TRIAL DATA SET**

| **Data Category** | **Information** |
| --- | --- |
| Sponsor(s) | HNE Health, University of Newcastle |
| Contact for public and scientific queries | Dr Ehsan Mahmoodi, associate investigator  Tel: 02 49213000 or 0421380528 Email: jhcardiologyreasearch@hnehealth.nsw.gov.au |
| Public title | Antiarrhythmic effects of phenytoin or dantrolene in patients with cardiomyopathy |
| Scientific title | Antiarrhythmic properties and safety of phenytoin or dantrolene in patients with cardiomyopathy; a randomised, double blinded, placebo controlled trial |
| Countries of recruitment | Australia |
| Universal Trial Number (UTN) | U1111-1232-2730 |
| Health condition(s) or problem(s) studied | Arrhythmia, Heart failure with reduced ejection fraction |
| Intervention(s) | Active comparators: phenytoin and dantrolene  Placebo comparator: matching capsules containing no active ingredients |
| Key inclusion and exclusion criteria | **Inclusion criteria:**   * Patients with cardiomyopathy, EF<35% * ICD or CRT * Aged 18 to 85   **Exclusion criteria:**   * Pregnant or breastfeeding females * Childbearing age women (not on 2 contraceptive methods including non-oestrogen based OCP) * Childbearing age women on oestrogen based OCP * Inability to provide informed consent * Patients with end stage kidney disease (eGFR<30) and patients on Dialysis * Liver cirrhosis * Patients with Aspartate transaminase (AST), and alanine transaminase (ALT) ≥ 3 times upper limit of institutional normal value (ULN) on 2 measurements separated by at least 5 days * Being prescribed the drug verapamil |
| Study type | Interventional Allocation: randomised Intervention model: parallel assignment Masking: double blinded (subject, caregiver, investigator, outcomes assessor) |
| Date of first enrolment | April 2019 |
| Target sample size | 105 |
| Primary objective | * To determine the safety, tolerability and dosing of long term use of phenytoin and dantrolene in patients with heart failure |
| Secondary objective | * To determine if phenytoin or dantrolene reduce the recurrence of ventricular arrhythmia in patients with cardiomyopathy compared to placebo * To determine the effects of dantrolene and phenytoin on heart failure symptoms |

## **PROTOCOL VERSION**

|  |  |
| --- | --- |
| Issue Date: | 24/4/2019 |
| Protocol amendment number: | 4 |
| Author(s): | Dr Ehsan Mahmoodi, Dr Nicholas Jackson |

### **ROLES AND RESPONSIBILITIES**

Principal Investigator: Dr Nicholas Jackson

Associate Investigators: Professor Andrew Boyle, Professor Derek Laver, and Dr Ehsan Mahmoodi

Data Safety Monitoring Board (DSMB): Dr Stuart Turner, and Dr Bradley Wilsmore

1. **LIST OF ACRONYMS AND ABBREVIATIONS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Abbreviation** | | **Definition** | |
| AAD  AE | | Antiarrhythmic Drug  Adverse Event | |
| ALP | | alkaline phosphatase | |
| ALT | | alanine aminotransferase | |
| ANCOVA | | Analysis of Covariance | |
| AST | | aspartate aminotransferase | |
| HF | | Heart Failure | |
| HFrEF | | Heart Failure with reduced Ejection Fraction | |
| BUN | | Blood urea nitrogen | |
| CNS | | Central nervous system | |
| CRF  CRT  CPI | | Case Report Form  Cardiac Resynchronization Therapy  Coordinating Principal Supervisor | |
| DSMB | | Data Safety Monitoring Board | |
| ECG | | Electrocardiogram | |
| eGFR | | estimated glomerular filtration rate | |
| EPS | | Electrophysiology Study | |
| FAS | | Full Analysis Set | |
| GGT | | gamma glutamyl transferase | |
| ICD | | Implantable Cardioverter Defibrillator | |
| ITT | | Intent-to-Treat | |
| IV | | Intravenous | |
| kg | | Kilogram | |
| Mg  µg | | Milligram  Microgram | |
| MI | | Myocardial infarction | |
| min | | Minute | |
| mITT | | Modified Intent to Treat | |
| mL | | Millilitre | |
| NYHA  OCP  NSVT | | New York Heart Association  Oral Contraceptive Pill  Nonsustained Ventricular Tchycardia | |
| PAD | | Pharmacologically active dose | |
| PCEs | | polychromatic erythrocytes | |
| PCI | | Percutaneous coronary intervention | |
| PI | | Principal Investigator | |
| PICF | | Participant Information and Consent Form | |
| PT | | prothrombin time | |
| PPM  PI | | Permanent Pacemaker  Principal Investigator | |
| RyR | | Ryanodine Receptor | |
| RBC | | Red blood cell | |
| SAE | | Serious Adverse Event | |
| SAP | | Statistical Analysis Plan | |
| SR | | Sarcoplasmic Reticulum | |
| ULN | | Upper limit of normal | |
| Um  VF  VT | | Micromole  Ventricular Fibrillation  Ventricular Tachycardia | |

# 

# **INTRODUCTION**

## **6. BACKGROUND AND RATIONALES**

Heart failure (HF) is complex disorder that involves changes in expression of calcium (Ca2+) handling proteins, Ca2+ dynamics and tissue remodelling. Tissue level changes in heart failure often include fibrosis, while changes within cardiomyocytes often affect structures critical to excitation-concentration coupling, including the ryanodine receptor (RyR), the associated protein junctophilin-2 (JPH2) and the transverse tubular system architecture. Evidence suggests that abnormal channel gating of RyR2 is a major cause for cardiac dysfunction, lethal arrhythmia and remodelling in heart failure. Exaggerated Ca2+ leak from the sarcoplasmic reticulum through RyR2 into the cytoplasm in failing cells has been linked to reduced sarcoplasmic reticulum (SR) Ca2+ content and depressed contractile function, elevation of resting Ca2+ levels and impaired relaxation, pro-arrhythmic early and delayed after-depolarizations, and energetic inefficiency as Ca2+ is redundantly cycled. (1)

Phenytoin has long been used to treat epilepsy and for some time as an antiarrhythmic medication. It was shown to have class IB antiarrhythmic drug (AAD) properties and an extensive literature supporting its effectiveness in the treatment of atrial and ventricular arrhythmias were published for many years. However, its use in treating arrhythmias has become obsolete in recent years due to the arrival of newer antiarrhythmic drugs (AADs).

Professor Laver and his group at Newcastle University recently showed that dantrolene causes up to 50% inhibition of RyRs and the dose response follows a hyperbolic inhibition curve. They then proved that both ethitoin and phenytoin could cause up to maximum 50 % inhibition of RyR2 channel in a manner paralleling that of dantrolene, and normalises SR Ca2+ release in cardiomyocytes from failing sheep hearts. This will improve contractility and reduce the diastolic leakage of calcium without affecting the systolic release of Calcium. (2)

With regards to dantrolene, there are a number of human and animal studies proving the efficacy of dantrolene in controlling arrhythmias (3-5). The long-term use of dantrolene has also been shown to be safe in the study by Mahmoud Bokhari and his colleagues (6).

We are now in a position to explore the factors affecting the actions of phenytoin, dantrolene and related compounds on human RyR2 in a clinical setting. The aim of this study is to investigate the effects of phenytoin and dantrolene in patients with heart failure and their potential to prevent ventricular arrhythmias and improve heart failure symptom.

This is unique concept of using RyR2 blocking agents (phenytoin and dantrolene) in failing hearts in order to prevent arrhythmias and heart failure symptoms.

## **7. OBJECTIVES**

7.a PRIMARY OBJECTIVE

* To determine the safety, tolerability and dosing of long term use of phenytoin and dantrolene in patients with heart failure

7.b SECONDARY OBJECTIVE

* To determine if phenytoin or dantrolene reduce the recurrence of ventricular arrhythmia in patients with cardiomyopathy compared to placebo
* To determine the effects of dantrolene and phenytoin on heart failure symptoms

## **8. STUDY DESIGN**

This is a randomised, double blinded, placebo controlled trial to assess antiarrhythmic properties of phenytoin and dantrolene, their efficacy and safety for treating arrhythmias and heart failure.

The study will compare all the 3 arms together: phenytoin versus dantrolene, phenytoin versus placebo and dantrolene versus placebo.

Randomisation will occur after consent is obtained and on enrolment into the study, participants will be randomised in a 1:1:1 ratio to receive phenytoin, dantrolene, or placebo.

# **METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES**

## **9. STUDY SETTING**

The participant recruitment will be through the cardiology outpatient clinic at john Hunter Hospital, Hunter Heart clinic, and the cardiology device clinic at John Hunter Hospital, Newcastle, NSW, Australia.

## **10. ELIGIBILITY CRITERIA**

Only participants who meet all of the inclusion and none of the exclusion criteria will be eligible to participate in the study:

10.a INCLUSION CRITERIA

* Patients with cardiomyopathy, EF<35%
* ICD or CRT
* Aged 18 to 85

10.b EXCLUSION CRITERIA

* Pregnant or breastfeeding females
* Childbearing age women (not on 2 contraceptive methods including non-oestrogen based OCP)
* Childbearing age women on oestrogen based OCP
* Inability to provide informed consent
* Patients with end stage kidney disease (eGFR<30) and patients on Dialysis
* Liver cirrhosis
* Patients with Aspartate transaminase (AST), and alanine transaminase (ALT) ≥ 3 times upper limit of institutional normal value (ULN) on 2 measurements separated by at least 5 days
* Being prescribed the drug verapamil

## **11. INTERVENTIONS**

11.a INTERVENTIONS

All the eligible patients will be invited to meet with the investigator (Ehsan Mahmoodi) to discuss involvement in the study. The regular clinician involved in reviewing participants will contact one of the investigators (Ehsan Mahmoodi) to attend the clinic. The investigator (Ehsan Mahmoodi) then will explain to the patients the details of the study and ask whether he/she is interested in participating. Recruitment documentation including Participant Information and Consent Form (PICF) will be provided at this time. All questions will be answered at the same visit and the patients will be asked if they are interested in participating. Any extra time will be given as per the patients request if they wish to think and consult next of kin, family members or friends in order to make their decision and consider participation in the study. The investigator (Ehsan Mahmoodi) will contact the patients who wish to consider participation and invite them to come for the screening visit. The patients who are interested to participate will be assessed again for eligibility at the screening visit. The Investigator (Ehsan Mahmoodi) will be obtaining the signed consent form and the participant information sheet.

After enrolling the required number of participants, we then proceed to randomisation. The study is a parallel-randomised controlled trial, with equal numbers of participants randomised to the intervention (phenytoin and dantrolene) and control (placebo) arm.

The participants then will be followed in a 2 month interval visits. The visit numbers can increase if there are any concerns regarding the procedure or medication adverse effects (AEs).

Participants will have Six-Minute Walk Test (6MWT) at the screening visit, 6 months visit and the last visit of the study. Studies showed the 6MWT is a reliable tool for evaluation and quantification of functional capacity in patients with heart failure (7, 8). We anticipate that there will be a learning effect in the placebo arm and there might be some improvement in this group 6MWT results. We therefore, will be looking for a greater improvement in the treatment arms.

11.b ADHERENCE

Face-to-face adherence reminder sessions will take place at the initial product dispensing and each study visit thereafter. This session will include:

1. Instructions about taking study pills including dose, timing, storage, and importance of taking pills regularly, and what to do in the event of a missed dose

2. Notification that there will be a pill count at every study visit

3. Importance of contacting the investigators if experiencing problems possibly related to study product such as symptoms of AEs or should they have any queries regarding the study progression

Participants are required to contact the study investigators immediately if they experience any of the following symptoms, which could indicate high serum concentration of the medications. These symptoms include: Nystagmus, dizziness, dysarthria, ataxia, tremor, drowsiness, involuntary movements, and seizure.

Subsequent sessions will occur at the follow-up visits. Participants will be asked about any problems they are having taking their study pills. There will be brief discussion of reasons for missed doses and simple strategies for enhancing adherence, e.g., linking pill taking to meals or other daily activities. Participants will have an opportunity to ask questions and key messages from the initial session will be reviewed as needed. Participants will return the unused tablets and bottle at each follow-up visit. Unused tablets will be counted and recorded on the appropriate CRF (Case Report Form).

10. c CONCOMITTANT CARE

Any concomitant medications taken must be documented in the participant notes and the Case Report Form (CRF). This record should include the drug name, the dose and frequency, route of administration, the start and stop date of administration, and the indication. All the over the counter and herbal medications will be recorded in the CRF. The standard of care medications will remain unchanged unless the participant’s primary care provider decides otherwise. It will be communicated and documented on the participant’s regular follow up reviews.

## **12. OUTCOMES**

12.a PRIMARY ENDPOINT

* Safety, tolerability and dosing to maintain therapeutic serum levels

12.b SECONDARY ENDPOINTS

* The occurrence of Ventricular arrhythmias (VT or NSVT of at least three beats duration, > 120 bpm) as detected by defibrillator.
* Repeat hospitalisation.
* Death.
* Heart failure symptoms and 6-minute walk distance.

## **13. PARTICIPANT TIMELINE**

The participants will be on the study for twelve months. Following the completion of the enrolment, the participants will be invited for the screening visit when they will be randomized to the control and treatment arms. They will then be followed in a two monthly basis. The details of follow up visits are as follows:

13.a SCREENING VISIT

The purpose of the Screening visit is to confirm participant eligibility against inclusion and exclusion criteria. Once written informed consent has been obtained, the following visit assessments and procedures will be performed:

* Review eligibility criteria
* Record participant demographic data
* Record participant medical history and medications
* Baseline blood tests including full blood count, liver function test and biochemistry profile,(Aspartate transaminase (AST), and alanine transaminase (ALT) should be ≤ 3 times upper limit of institutional normal value (ULN) on 2 measurements separated by at least 5 days)
* Observations
* Device interrogation
* Upon confirmation of eligibility and suitability to proceed, participants will be randomised
* Participants will be commenced on trial medications as per their allocations
* Baseline Six-Minute Walk Test (6MWT)
* Assessment of any signs of depression and suicidal ideation

13.b MONTHS 2, 4, 6, 8, 10 / EARLY TERMINATION

Repeat blood tests (liver function test and biochemistry profile, medications serum level) and device data collection will be performed prior to office visits at 2, 4, 6, 8, and 10 months. At these office visits, blood test results, occurrence of ventricular arrhythmia, heart failure symptoms (assessed by New York Heart Association (NYHA) functional class and Minnesota Living with Heart Failure Questionnaire) and medications adverse effects will be reviewed. Participants will also be assessed for any signs of depression or suicidal ideation at each follow up visit.

Participants will be asked to raise any questions or concerns. The investigators will make sure all the questions and concerns are adequately addressed before the end of the visit.

Participants who withdraw from the study prior to completion of the treatment period should be asked to return to the site for a final follow up visit, and have the 12-month visit performed.

13.d MONTH 12/END OF STUDY

Participants will return to the site the final assessment including Six-Minute Walk Test, device interrogation, blood tests, medication serum level, burden of the arrhythmia at the visit time, any signs of depression or suicidal ideation, and heart failure symptoms (assessed by New York Heart Association (NYHA) functional class and Minnesota Living with Heart Failure Questionnaire).

13.e WITHDRAWL OF PARTICIPANTS

Participants can terminate their study participation at any time and without giving a reason, without prejudice to further treatment. Participants who discontinue from the trial should always be asked about the reason(s) for their discontinuation and about the presence of any AEs. If possible, they should be seen and assessed by an investigator and have an Early Termination Visit. AEs should be followed up until resolved or stable and determined to be chronic.

The Investigator or treating physician can exclude a participant from continuing in the trial.

Possible reasons for discontinuing a participant may include:

* Participant withdrawal of consent
* Any unacceptable AEs, in the judgement of the Investigator
* Participant non-compliance with the protocol

Figure 1.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **STUDY PERIOD** | | | | | | |
|  | **Screening** |  | **Monitoring period** | | | | **Close-out** |
| **TIMEPOINT** | **Day 1** | **2 Month** | **4 months** | **6 months** | **8 months** | **10 months** | **12 months** |
| Record participants information | X |  |  |  |  |  |  |
| Eligibility screen | X |  |  |  |  |  |  |
| Informed consent | X |  |  |  |  |  |  |
| Concomitant medication assessment | X | X | X | X | X | X | X |
| Allocation | X |  |  |  |  |  |  |
| Phenytoin |  |  |  |  |  |  |  |
| Dantrolene |  |  |  |  |  |  |  |
| Placebo |  |  |  |  |  |  |  |
| Device interrogation, blood tests prior to visit |  | X | X | X | X | X | X |
| observations |  | X | X | X | X | X | X |
| Adverse effects, Medication serum level |  | X | X | X | X | X | X |
| 6MWT | X |  |  | X |  |  | X |

## **14. SAMPLE SIZE**

With regards to the power calculation, there was not enough data on the effects of phenytoin and dantrolene on heart failure symptoms. As a result, the power calculation was done on the basis of capacity of phenytoin to reduce arrhythmia in heart failure. In 1999, Meissner et al. showed that dantrolene sodium improves the negative force-frequency relationship and beta-adrenergic responsiveness in failing human myocardium (9). Hartman et al. in their study showed that dantrolene reduces the pro-arrhythmogenic diastolic calcium leakage through sarcoplasmic reticulum calcium) in human diseased atrial and ventricular cardiomyocytes (10). In another study by Kobayashi et al. it was shown that dantrolene corrects defective inner-domain interactions within RyR2 in failing hearts, inhibits spontaneous Ca2+ leak, and improves cardiomyocytes function in failing hearts and may have a potential to treat heart failure(5). Epstein et al. in their trial showed after 26 months follow up, there were 70% rate of recurrence of ventricular arrhythmia in the group of patients not on phenytoin and 30% recurrence rate of ventricular arrhythmia in the patient group on Phenytoin(11). Sample size of 105 participants will create >80% power to detect the significance, with a type 1 error rate of 0.05, using the Fisher’s exact method.

105 participants will be enrolled and randomised in a 1:1:1 ratio to one of 3 arms:

* 35 will receive phenytoin
* 35 will receive dantrolene
* 35 will receive placebo

## **15. RECRUITMENT**

Participants will be screened from different places:

* Patients with ischaemic or non-ischaemic HFrEF with ICD or CRT, referred to John Hunter Hospital PPM/ICD clinic with NSVT, VT VF diagnosed from the device interrogation
* Patients with ischaemic or non-ischaemic HFrEF with ICD or CRT attending their follow up to the electrophysiologist room at John Hunter Hospital outpatient clinic
* Patients with ischaemic or non-ischaemic HFrEF with ICD or CRT attending the device check appointment

## **16. ALLOCATION**

Participant eligibility will be established before randomisation. Eligible participants will be assigned to phenytoin, dantrolene or placebo in a 1:1:1 ratio according to the randomisation schedule.

A statistician blinded to the identity of participants, using computer-generated random numbers, will perform randomisation. An interactive web (or voice) system (IW/VRS) will be used to allocate participants to different arms according to the schedule.

## **17. BLINDING (MASKING)**

Trial participants, care providers, study investigators, data collectors and outcome assessors or committees will be blinded.

### 17.a Emergency unblinding

In order to maintain the overall quality and legitimacy of the clinical trial, code breaks will only occur in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient.

# **METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS**

### **18. DATA COLLECTION METHODS**

Authorised study site personnel designated by the Investigator will complete data collection and entry. This will include principal investigators and members of the existing clinical trials and research team at John Hunter Hospital. Appropriate training and security measures will be completed with the Investigator and all authorised study site personnel who have not already completed these, prior to the study being initiated and any data being entered into the system for any study participants.

All data must be entered in English. The CRFs should always reflect the latest observations on the participants in the trial; therefore, the CRFs are to be completed as soon as possible after the participant’s visit. The Investigator must verify that all data entries in the CRFs are accurate and correct. Every effort will be made to accurately document symptoms, medication use/changes and arrhythmia measured recurrence at each follow-up. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the CRF. The Investigator will be required to sign off on the clinical data.

## **19. DATA MANAGEMENT**

Participants will be asked to provide written consent to the collection of their identifying data. Data linkage will be used in this study. Following linkage, identifying data will be stored separately from the study database. All research documentation will be labelled with a unique person number, as an identifier and any potentially identifiable information will be removed. This data needs to be re-identifiable in order to link with follow-up data. The intervention is conducted in the clinical setting, and clinicians will record and store data according to standard professional guidelines and confidentiality practices.

**20. ARCHIVING AND PUBLICATION**

The PI is responsible for the archiving of the trial records for their site. Trial records include the participant files as well as the source data, the Investigator Site File, and other study documents. Trial records must be archived for at least 15 years. However, these documents should be retained for a longer period if specified by regulatory requirements.

If the PI leaves the investigational site for whatever reason, the responsibility for all study related records must be transferred to another person at the site.

Patients who withdraw from the study will be asked if they would consent to continue completing follow-up measures and for any of their existing data to be included in analysis. If consent is not given any electronic or paper records pertaining to their involvement will be erased and destroyed**.** An investigator may publish any data related to this study (poster, abstract, paper, slide presentation, etc.)

## 

## **21. STATISTICAL METHODS**

21.a ANALYSIS

* Full analysis set (FAS): All participants randomised into the study. Participants will be analysed according to the intervention to which they were randomised. Efficacy analyses performed in the FAS are considered supportive of analyses performed in the mITT set.
* Modified Intention-to-treat (mITT) set: All randomised participants who had an intervention. Participants will be analysed according to the intervention to which they were randomised. The primary efficacy analysis will be performed in the mITT set.

21.b STATISTICAL ANALYSIS PLAN

All efficacy and safety data will be listed and summarised using descriptive statistics by treatment group with continuous variables will be reported as mean ± standard deviation or as median and percentiles, and categorical variable reported as counts and percentages. The primary analysis will be in the FAS, further details on the handling of withdrawals and/or missing data will be specified in the SAP. The percentage of time spent free of Arrhythmia over the 12-month follow-up will be compared between groups using a Fine and Gray proportional hazard regression model. The outcome in the model will be time from randomisation to detection of arrhythmia (either device detected or symptomatic hospital admission), Deaths will be considered as a competing risk, observations being censored if no event has occurred by 12 months. The model will include treatment arms, with the placebo arm as the referent group. The two active treatment arms will be compared to placebo arm (with sub-hazard ratio, 95% confidence interval and p-value). The two active treatments will be compared against each other if both treatments are statistically significantly different to placebo (at 5% sig). Sensitivity analyses of the primary endpoint will be performed in the FAS to assess the impact of missing data on the robustness of the primary analysis. This analysis will also be repeated in the PP set. All statements of statistical significance will be based on a two-sided test at the 5% level of significance, unless stated otherwise. Further details will be specified in the SAP. Any deviations from the planned analyses detailed in the protocol will be documented in the SAP and final study report. If the study is prematurely discontinued, all available data will be listed and a review will be carried out to determine which statistical analyses are considered appropriate.

# 

# **Methods: Monitoring**

**22. DATA AND SAFETY MONITORING BOARD (DSMB)**

An independent Data Safety Monitoring Board (DSMB) including Dr Bradly Wilsmore, and Dr Stuart Turner will review safety data and provide independent oversight of participant safety. They will review the study at month 1, 6 and the end of the study. Dr Oldmeadow will also advise on the statistics and data analysis.

## **23****. SAFETY AND TOLERABILITY**

Safety and tolerability will be assessed by:

* Discontinuation of subject due to a serious adverse event (SAE) or discontinuation of subject due to an extreme laboratory parameter.
* Dose adjustment during the treatment period; and/or non-adherence to randomised treatment
* Number of SAEs
* Time to first appearance of AEs
* Time to dose adjustment

Participants will be questioned and monitored at all the visit times with regard to any AEs they may have experienced. Participants are required to contact the study investigators if there are any symptoms of possible AEs. The investigators then will decide if they need to organise another visit.

## **24. HARMS/ ADVERSE EVENTS**

AEs data will be listed individually and incidence of AEs summarised by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE, based on preferred terminology defined by Medical Dictionary for Regulatory Activities (MedDRA; Version 13.1, or later), will be counted only once for a given participant. A summary of the number and percent of participants with the following treatment emergent AEs will be displayed by treatment groups:

* All AEs
* Intervention-related AEs
* Severe AEs
* AEs leading to discontinuation of the study or cross-over

The definitions of AEs and SAEs are given below. It is extremely important that all staff involved in the trial are familiar with the content of this section. The PI is responsible for ensuring this.

ADVERSE EVENT DEFINITIONS

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered the study treatment and which does not necessarily have a causal relationship with this strategy. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product.

Laboratory reference ranges are defined by upper or lower limits of parameters of the laboratory. The Investigator should ensure that each parameter out of the normal range is assessed for clinical significance and potential for being an AE. It is at the discretion of the Investigator to document any change in laboratory result as an AE if he considers the change to be clinically significant, even if the absolute value is within the alert limit or reference range.

The participant must be instructed to inform the Investigator about all AEs and these must be documented in the participant records and Case Report Form (CRF) together with their intensity;

* Severe are those AEs, which make normal daily routine impossible
* Moderate AEs impact the normal daily routine
* Mild AEs do not impact normal daily routine.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilised for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

The Investigator must assign causality to each adverse event based on the following scale:

* Not related: AE for which there is evidence of another explanation, e.g. the adverse event is obviously explained by the participant’s disease(s), is in accordance with the known effect of a concomitant medication, or has occurred prior to commencement of the study period.
* Unlikely related: AE with a time to study commencement that makes a relationship improbable (but not impossible), and disease or other drugs provide plausible explanations.
* Possibly related: AE with a reasonable time relationship to study commencement, which could also be explained by disease or other drugs.
* Probably related: AE with reasonable time relationship to study commencement that is unlikely to be attributed to disease or other drugs.
* Definitely related: AE with plausible time relationship to study commencement, which cannot be explained by disease or other drugs.

All AEs must be documented by the Investigator, regardless of causality.

Expected AEs are defined as all AEs stated in the IB. If an AE has not been previously reported (including type, degree, or frequency) in the IB, it is an unexpected adverse event.

If an AE leads to premature discontinuation of the study, the appropriate pages of the CRF must be completed.

SERIOUS ADVERSE EVENTS (SAES)

An AE shall be classified as serious if it:

* Results in death.
* Is life-threatening. 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.
* Requires in-patient hospitalisation or prolongation of existing hospitalisation. Hospitalisation is defined as in-patient admission or care regardless of duration. Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Elective surgery, hospitalisation for social reasons (with no causal AE), or hospital admissions and/or surgical operations planned before or during this study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
* Results in persistent or significant disability/incapacity.
* Is a congenital anomaly/birth defect.
* Is an important medical event. This includes events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed above.

RECORDING OF ADVERSE EVENTS

AEs will be captured from the time of informed consent until the final study visit. Participants will be asked at each visit whether they have experienced any AEs. If a participant has concerns over ongoing symptoms or events. The participants are required to contact the investigators in between the visits if there are any possible symptoms of adverse effects. The investigator then will decide whether they need to organise another visit for the patients.

It is preferable that AEs are reported as diagnoses if one can be made, rather than individual signs and symptoms. The AE description, start and stop dates, intensity, causality and outcome must be recorded, as well as any actions taken.

Unless a diagnosis is made, or signs and symptoms are present, laboratory values or vital signs abnormalities should only be reported as AEs if they cause the participant to discontinue from the trial, the investigator feels it is clinically significant, or they meet a criterion for a SAE.

REPORTING OF SERIOUS ADVERSE EVENTS

The investigational site must report follow-up information on SAEs within 24 hours. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within 24 hours.

All SAEs will be recorded in the participant records and the CRF.

The investigator must notify their Independent Ethics Committee (IEC) of any SAEs occurring at their site, within the time period specified by the IEC.

FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All AEs and all SAEs must be followed by the Investigator until resolution, until the AE stabilises or is recognised as a permanent condition by the Investigator, or until the participant is lost to follow up, whichever comes first. Follow-up investigations may be necessary according to the Investigator’s medical judgement.

**25. SIX-MINUTE WALK TEST (6MWT)**

The six-minute walk test (6MWT) is a simple, low cost, reliable, and valid method for evaluating the functional capacity of cardiac patients

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include unstable angina and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Possible complications include: angina, dyspnea, and/or intense fatigue, nausea, profuse sweating, palpitations, dizziness, signs of diminished tissue perfusion (pallor, cyanosis, pre-syncope); drop in BP (greater than 10 mmHg), and absence of a minimal increase in HR (less than 10 bpm).

**26. PHENYTOIN**

Phenytoin is an old antiepileptic agent but still used widely for the treatment of focal and generalized seizures, status epilepticus, and as a second-line agent for patients with mixed seizures. It was used for many years in treating atrial and ventricular arrhythmias and there is an extensive literature available, supporting its effectiveness. In most studies, which used phenytoin as an antiarrhythmic agent, the dosage of phenytoin was 5-10 mg/kg with the targeted phenytoin serum level of 10-20 µg/ml. This is in keeping with the data suggesting the therapeutic blood level of phenytoin for the treatment of most ventricular arrhythmias is generally between 10- 18 µg/ml. (12)

Our recommended starting dosage for phenytoin is 5mg/kg/day, oral, in three divided doses. A period of 7 to 10 days is required to achieve therapeutic blood levels. In 2 weeks intervals, the medication serum level will be checked and the dose will be adjusted (Increase in 1mg/kg/day increments with maximum dose of 8 mg/kg/day if the level is too low or reduce the dose if the level is too high) until the targeted therapeutic level of 10-20 µg/ml is achieved*.*

ELDERLY PATIENTS, PATIENTS WITH RENAL OR HEPATIC DISEASE

It is anticipated that these group of patients will need less dose escalation but no specific monitoring will be required.

PATIENTS ON AMIODARONE

In patients taking amiodarone, we will start with a 25% lower dose of phenytoin.

CONTRAINDICATIONS

Phenytoin is contraindicated in patients with a history of hypersensitivity to phenytoin, or other Hydantoin products, or other inactive ingredients in this product.

Phenytoin crosses the placenta and it is contraindicated in pregnancy.

ALCOHOL USE

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels. In this study, we encourage the participants to remain abstinent form alcohol during the trial.

SIDE EFFECTS

Common adverse effects of phenytoin (> 1%):

* Nausea and vomiting,
* insomnia,
* agitation,
* sedation,
* confusion,
* ataxia,
* nystagmus, diplopia, blurred vision,
* vertigo,
* behavioural disturbances,
* impaired learning (dose-related),
* gingival hypertrophy,
* skin eruption,
* coarse facies,
* hirsutism (long-term use),
* Increased liver enzymes (usually not clinically important): phenytoin is mainly metabolised in liver. Increase in transaminases more than three folds will be considered significant.

Other side effects of phenytoin (rare<0.1%):

* Phenytoin can increase the risk of suicidal thoughts or behaviour. In this study, Patients will be monitored in all follow up visits for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Cases of bradycardia and asystole/cardiac arrest have been reported, most commonly in association with phenytoin toxicity, but also at recommended phenytoin doses and levels. In the present trial, all the participants have a device (ICD/CRT) and any arrhythmias will be recorded. We monitor the medication serum levels, liver function test, full blood count and patient’s biochemistry panel on a regular the dose will be adjusted or the drug will be stopped if indicated.

* Phenytoin can cause rare, severe cutaneous adverse events such as Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients are required to be alert for the signs and symptoms of skin rash and blisters, fever, and itching and should seek medical advice from the study investigator immediately when observing any indicative signs or symptoms.
* Phenytoin can rarely cause angioedema.
* There have been reports suggesting the development of lymphadenopathy (local or generalised) related to phenytoin. It could also cause thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. This will be monitored with regular FBC (Full Blood Count) before each follow up visits.
* Phenytoin may also raise the serum glucose level in diabetic patients.
* Phenytoin can cause hypoalbuminemia. In cases of low albumin we will measure free serum phenytoin level.
* Phenytoin can result in vitamin D deficiency.
* Intravenous administration of phenytoin can cause hypotension.

Phenytoin is considered to be a safe medication in clinical trials. In studies evaluating patients with toxic effects of oral phenytoin, it was shown that none of those patients developed a cardiovascular adverse effect or a serious electrocardiographic changes. They also showed those toxicities was found at the serum phenytoin level almost twofold of the upper therapeutic level (13, 14). In another study by Guldiken et al. they performed a systematic review on the cardiovascular adverse effects of phenytoin and they concluded that phenytoin is safe in both oral administration and the IV administration at a maximum infusion rate of 50 mg/min in young patients and a rate of 25 mg/min in patients older than 50 years.(15)

INTERACTIONS WITH OTHER MEDICATIONS

In general, phenytoin is a potent inducer of the hepatic cytochrome P450 microsomal isoenzymes. There are other factors affecting a patient’s susceptibility to enzyme-inducing interactions which include age, cigarette smoking or the presence of liver disease.

There are many drugs that may increase or decrease phenytoin levels or that phenytoin may affect. We will try to minimise the drug-interactions, by regular checking serum phenytoin concentrations. We will modify the medication dose or stop the drug based on the regular blood tests results (Full blood count, biochemistry panel, liver function test, and phenytoin serum level) and the occurrence of the AEs. With regards to this study and the participants with cardiomyopathy and arrhythmias, the expected common antiarrhythmic medication will include amiodarone.

There have been studies done on amiodarone and phenytoin interactions and they showed that concomitant use of amiodarone and phenytoin results in reduction of phenytoin clearance. Nolan and his colleagues in their study showed there is a significant increase in serum phenytoin concentrations when daily low-dose amiodarone treatment was administered in conjunction with phenytoin dosing to steady-state. They suggested the steady-state doses should be reduced at least 25% when amiodarone is concurrently administered (16). There are other reports that indicated amiodarone increased steady-state serum concentrations of phenytoin. (17) Therefore, in patients taking amiodarone, we will start with a 25% lower dose of phenytoin.

**27. DANTROLENE**

Dantrolene is a direct acting skeletal muscle relaxant and is indicated in controlling the manifestations of clinical spasticity resulting from serious chronic disorders such as spinal cord injury, stroke, cerebral palsy, or multiple sclerosis.

DOSAGE AND ADMINISTRATION

Dantrolene causes up to 50% inhibition of RyRs and the dose-response follows a hyperbolic inhibition curve with half maximal inhibition at about 0.2 micromole/L which is similar to that measured in cell homogenates and in cardiomyocytes (18). Hartman et al in their study showed that the specific action of dantrolene on human atrial and ventricular RyR2 is seen at a concentration of 10 micromole/L without influencing repolarisation, which underscores the attractiveness of this drug for antiarrhythmic treatment (10) A number of other human studies concluded that 10 micromole/L is the clinically effective described concentration of dantrolene (19, 20).

Moreover, in most studies on dantrolene, there were no toxicities reported at the dantrolene concentration level between 1-10 micromole/L, therefore, our targeted therapeutic level will be 1-10 micromole/L.(5, 21, 22)

Our starting dose is 25 mg, three times a day, oral. The patients will have dantrolene serum concentration on a two-weekly basis and the dose will be adjusted until the targeted concentration of 1-10 micromole/L is achieved (The dose will be reduced if the level is too high and will be increased if the level is too low).

CONTRAINDICATIONS

Dantrolene is contraindicated in acute hepatitis and active cirrhosis, it should be used with caution in patients with impaired pulmonary function, particularly those with obstructive pulmonary disease. In MIMS, dantrolene is listed to be used with caution in patients with severely impaired cardiac function, however, this is likely to be secondary to hypo perfusion and impaired renal function which will be overcome by our approach to start low dose and monitor the serum concentration on a two weekly basis to adjust the dose if required.

PRECAUTIONS

* Dantrolene causes dizziness, drowsiness, and weakness; alcohol and other sedative medications may intensify this effect. Patients will be cautioned against driving a motor vehicle or participating in hazardous occupations while taking dantrolene.
* In this study, we encourage the participants to remain abstinent form alcohol during the trial.

SIDE EFFECTS

Common adverse effects of dantrolene include (have been experienced by approximately 20 % of patients):

* drowsiness,
* dizziness,
* weakness,
* general malaise,
* fatigue,
* Diarrhoea. If severe, it will require a temporary withdrawal of dantrolene therapy. If diarrhoea recurs upon readministration, it should be stopped permanently.

Less common adverse effects of dantrolene:

* Dantrolene can cause photosensitivity reaction; patients will be cautioned about exposure to sunlight while on therapy.
* Dantrolene can cause hepatotoxicity which appears to be dose related and seen in doses above 200 mg/day. It is also more common in women over 35 years of age receiving concomitant oestrogen therapy. We will monitor the participants with regular liver function tests and dantorlene serum concentration. Increase in transaminases more than three folds will be considered significant. Childbearing age women on oestrogen based OCP will be excluded from the study.
* Dantrolene can cause tachycardia and erratic blood pressure.
* There are some reports of aplastic anaemia, anaemia, leukopenia, lymphocytic lymphoma, and thrombocytopenia related to dantrolene. The participants will have Full Blood Count before each follow up visit.
* Dantrolene may cause pleural effusion and pericarditis.

LONG TERM SAFETY

Bokhari and his colleagues recently screened the patients treated with chronic (>3 months) oral dantrolene, for muscle disorders, over the last 27 years in the Malignant Hyperthermia Clinic at Toronto General Hospital. They reported for the first time the safety of long term oral dantrolene use. During a mean of 10.9 +/- 6 years follow-up of oral dantrolene, no major cardiac events (serious arrhythmia, sudden death, or myocardial infarction) were noted. (6)

INTERACTIONS

While a definite drug interaction with oestrogen therapy has not yet been established, caution should be observed if the two drugs are to be given concomitantly. Therefore we will not include patients taking oestrogen-based oral contraception or hormone replacement therapy.

There are very rare reports of cardiovascular collapse in patients treated simultaneously with verapamil and dantrolene sodium. The combination of dantrolene sodium and calcium channel blockers, such as verapamil, is not recommended. The combination of therapeutic doses of intravenous dantrolene sodium and verapamil in halothane/ α-chloralose anaesthetised swine has resulted in ventricular fibrillation and cardiovascular collapse in association with marked hyperkalaemia. We have excluded patients taking verapamil.

With regards to this study, all the participants have a device (ICD/CRT) and any arrhythmias will be recorded. We monitor the medication serum levels, liver function test, full blood count and patient’s biochemistry panel on a regular the dose will be adjusted or the drug will be stopped if indicated.

# **ethics and dissemination**

## **28. RESEARCH ETHICS APPROVAL**

The protocol and the PICF will be submitted for approval to the HREC, and must be approved. Any amendment to the protocol will be sent to the HREC. No deviations from or changes to the protocol will be implemented without documented approval/favourable opinion from the HREC of an amendment, except where necessary to eliminate an immediate hazard to a trial participant, or when the changes involve only logistical or administrative aspects of the trial.

The deviations from or changes to the protocol which were implemented to eliminate an immediate hazard to a trial participant and the proposed amendment, if appropriate, will be submitted to the HREC for review and approval as soon as possible.

The PI will submit progress reports to the HREC according to local regulations and guidelines. The PI will also provide the IEC with any reports of SAEs from the trial site in accordance with the IEC requirements and timelines.

## **29. PROTOCOL AMENDMENTS**

If it is necessary for the trial protocol to be amended, the amended protocol must be approved by the IEC, unless the immediate safety of participants is involved.

If a protocol amendment requires a change to the PICF, approval of the revised PICF by the IEC is required before the revised form can be used.

## **30. CONFIDENTIALITY**

The PICF will explain that trial data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. This database will identify participants only with ID number. The PICF will also explain that for data verification purposes IECs or sites may require direct access to parts of the hospital or site records relevant to the trial, including personal participant information. Safeguards will be in place to protect confidentiality and anonymity of study participants. Only the study CIs, AIs, study staff and Research Project Manager will have access to completed data and other research documents. Any written documents will use ID numbers and computer databases will be password protected. Principles of confidentiality in the therapist-patient relationship stand for all participants in the study throughout the intervention.

All material will be kept in a locked filing cabinet, in a locked office, in a secure University/Hospital building. All electronic data will be stored on a computer network system maintained at the cardiovascular department, John Hunter Hospital, Newcastle, NSW.

## 

## **31. ACCESS TO DATA**

Personnel with access to the data**:**

1. The Investigators named in this application - to monitor process of the study and for analysis purposes.
2. The study co-ordinators - monitoring of participation status and administrative purposes such as mail out of questionnaires and data entry.
3. Research Assistants - data entry of de-identified data.

**32. DISSEMINATION POLICIES**

This study information will be retained for fifteen years according to The Australian Code for the Responsible Conduct of Research states.

After the retention period, all available data will be disseminated. Digital information may be destroyed by digital file shredding, erasure via degaussing (i.e. using a magnetic field), physical destruction of storage media, or reformatting (only if guaranteed to be non-reversible). All back-ups will also be destroyed. Digital information (computer files) will be deleted through a process of repeated over-writing of the documents and deletion from the server, ensuring that the contents cannot be recovered.

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# **34. APPENDICES**

CASE REPORT FORM

Version: 4 (24/04/2019)

PROTOCOL Version: 4

Antiarrhythmic properties of phenytoin or dantrolene

|  |  |
| --- | --- |
|  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| **BASELINE SYMPTOMS** | | | |
| Syncope | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Dizziness | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Headache | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Nausea | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Anorexia | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Vomiting | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Diarrhoea | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Abdominal pain | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Chest pain | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Skin rash | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Urticaria | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Joint pain | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Muscle pain | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Palpitations | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Dyspnoea | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Hearing problem | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Confusion | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Visual blurring | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Fatigue | 1. Yes | 2. No | Duration: \_\_\_\_\_\_\_ days |
| Other symptom: | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | Duration: \_\_\_\_\_\_\_ days |
| Other symptom: | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | Duration: \_\_\_\_\_\_\_ days |
| Other symptom: | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | Duration: \_\_\_\_\_\_\_ days |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ADVERSE EVENTS *– make multiple copies of this page if required* | | | | | | | | |
| Adverse event name | |  | | | | | | |
| Intensity | | 1 Mild | | | 2 Moderate | | | 3 Severe |
| If SAE specify: | | 1 Death  2 Life-threatening  3 Persistent or symptomatic disability or incapacity  4 Hospitalisation or prolongation of hospitalisation  5 Congenital anomaly or birth defect  6 Other important medical event | | | | | | |
| Onset Date | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | D | D | M | M | M | Y | Y | Y | Y | | | | | | | | |
| End Date | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | D | D | M | M | M | Y | Y | Y | Y | | | | | | OR  Ongoing at the end of study | | |
| Therapy | 1 None  3 Other | 2 Drug  4 Drug and other | | | | | | |
| Action Taken with Study Drug | 1 Dose unchanged  4 Drug withdrawn  99 Not Known | 2 Dose reduced  5 Dose increased | | | | | 3 Drug temporarily interrupted | |
| Outcome | 1 Recovered  3 Recovering with sequelae  5 Fatal | | | 2 Recovering  4 Continuing  99 Not Known | | | | |
| Relationship to Study drug | 1 Certain  4 Unlikely | | 2 Probable  5 Not related | | | | 3 Possible  6 Unclassified | |

|  |  |  |
| --- | --- | --- |
| **MEDICATION HISTORY (within the last 7 days)**  - *Make multiple copies of this page if required* | | |
| **Medication Name** | **Start Date** | **Stop Date** |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **D** | **D** | **M** | **M** | **M** | **Y** | **Y** | **Y** | **Y** | |
| *OR*1 Unknown | *OR*1 Ongoing |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **BASELINE PHYSICAL EXAMINATION** | | | | | | | | | | | | | |
| Weight | |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | |  |  |  | . |  | kg | | | | | | | Height | | |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | |  |  |  | . |  | cm | | | | | |
| Temperature | |  |  |  |  |  | | --- | --- | --- | --- | --- | |  |  | . |  | °C | | | Method of Recording | | | | | | | | | Heart rate | |  |  |  |  | | --- | --- | --- | --- | |  |  |  | bpm | |
| Axillary | | Tympanic | | | Rectal | | Oral | |
| 1 | | 2 | | | 3 | | 4 | |
| Respiratory rate | |  |  |  | | --- | --- | --- | |  |  |  | | | | | | Blood pressure | | | | | |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | |  |  |  | / |  |  |  | mmHg | | | |
| Hepatomegaly | 1. Yes | 2. No | | |  |  |  | | --- | --- | --- | |  |  | cm |   If yes, size: | | | | | | | | | |
| Splenomegaly | 1. Yes | 2. No | | |  |  |  | | --- | --- | --- | |  |  | cm |   If yes, size: | | | | | | | | | |
|  | | **Normal** | | **Abnormal** | | | | **Specify if abnormal** | | | | | |
| Central Nervous System | | 1. | | 2. | | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | | | | | |
| Cardiovascular System | | 1. | | 2. | | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | | | | | |
| Respiratory System | | 1. | | 2. | | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | | | | | |
| Gastrointestinal System | | 1. | | 2. | | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | | | | | |
| Skin | | 1. | | 2. | | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | | | | | |
| Joints | | 1. | | 2. | | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | | | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **FINAL STUDY OUTCOME** | | | |
| **Subject has completed the study?** 1 | | **Completion date :** | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | D | D | M | M | M | Y | Y | Y | Y | |
| **If NOT completed specify last follow up date:** | | | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | D | D | M | M | M | Y | Y | Y | Y | |
| **Reason not completed:**  (Tick only **one** box) | 1 Significant non-compliance  2 Drug-related AE  3 Treatment failure  4 Consent withdrawn  5 Lost to follow-up  6 Other (specify) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | |
| **Remarks:** |  | | |
|  | | |
|  | | |
|  | | |
| **Investigator's Statement: I have reviewed the data recorded in this CRF and confirm that the data are complete and accurate**  **Investigator (Full name):** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  **Investigator Signed?** 1  **Signature Date:**   |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | D | D | M | M | M | Y | Y | Y | Y | | | | |