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Status migrainosus inpatient treatment with eptinezumab (SMITE): study protocol for a randomised controlled trial

Jason Charles Ray ,[1,2,3] Zhibin Chen,[3] Georgia Ramsay,[1] Jack Germaine,[1] Elspeth J Hutton[1,3]

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[1]Neurology, Alfred Health, Melbourne, Victoria, Australia
[2]Neurology, Austin Health, Heidelberg, Victoria, Australia
[3]Department of Neuroscience, Monash University Central Clinical School, Melbourne, Victoria, Australia

Correspondence to
Dr Jason Charles Ray;
j.ray@alfred.org.au

ABSTRACT

Introduction Status migrainosus is a disabling complication of migraine, which frequently results in hospitalisation. For patients who fail to respond to simple analgesia, triptans and intravenous prochlorperazine or chlorpromazine, there are limited treatment options, and a paucity of high-quality evidence to guide clinical practice. Eptinezumab, an intravenous monoclonal antibody specific for the calcitonin gene-related peptide ligand which achieves maximal plasma concentration immediately following administration and may improve migraines from day one. Intravenous lignocaine is an anaesthetic medication used in treatment of status migrainosus, often requiring prolonged admissions and with potential cardiac adverse events. The aim of this study is to assess the efficacy and safety of eptinezumab in the treatment of status migrainosus in comparison to intravenous lidocaine.

Methods and analysis Status migrainosus inpatient treatment with eptinezumab is a randomised, controlled, single-centre clinical trial conducted in a parallel design with an active comparator conducted in Melbourne, Australia. This study randomises forty patients (1:1) to receive either eptinezumab or an infusion of intravenous lignocaine for up to 5 days. It will assess the effect of eptinezumab compared with intravenous lignocaine in aborting status migrainosus, with the primary outcome of time from infusion until resolution of pain. It will explore several secondary measures including change in health resource utilisation, effect on patient reported outcomes of migraine disability and the safety and tolerability of each medication.

Ethics and dissemination This study has been reviewed and approved by the Human Research Ethics Committee of Alfred Health, local reference number 443/21, and all participants will provide informed consent for participation in the trial and dissemination of results.

Trial registration number The trial registration number is ACTRN12621001616864. The results of this study will be disseminated through peer-reviewed journals, conference presentations and social media.

Strengths and limitations of this study

- This study is the first controlled trial of eptinezumab in the treatment of status migrainosus, and will provide high-quality evidence for the treatment of status migrainosus
- Strengths of this study include its controlled design, which will increase the quality of data on status migrainosus, the use of an active control, which will provide clinically meaningful outcomes and the incorporation of patient-centred and health-economic outcomes.
- Limitations of this study include that it is a single-site study, the allowance of concomitant medications during the trial period and the paucity of high-quality data to guide statistical power analyses.

INTRODUCTION

Migraine is the leading cause of reversible disability in people under 50, affecting 1.3 billion people worldwide.[1] Accordingly, the health economic impact of migraine is substantial. Within Australia, headache is the 20th most common cause for admission to hospital with over 2.3 million admissions costing $A6.8 billion in 2018.[2]

Patients who present to hospital tend to have unremitting migraine attacks for greater then 72 hours that are termed 'status migrainosus'. Within Australia, headache was the 20th most common diagnosis for patients subsequently admitted to hospital, and less then 2% of emergency department (ED) presentations for headache are for secondary headaches.[2 3] Within the ED they will commonly receive simple analgesia, triptan and either chlorpromazine or prochlorperazine therapy. Current medical practice for second-line therapies includes a low-dose intravenous infusion of an anaesthetic agent; ketamine or lignocaine (lidocaine), which is recommended as a first-line or second-line treatment by 15% of clinicians surveyed by the American Headache Society.[4] This is supported by small retrospective case series, however, requires hospitalisation for up to

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5 days, has potential cardiac and neuro-psychiatric side effects and requires cardiovascular monitoring.[5 6]

On the basis of theUS Preventative Services Task Force Criteria, for patients who have failed triptan and prochlorperazine therapy, none of the current inpatient treatment options for status migrainosus have high-quality evidence.[7] With a single randomised trial for intravenous dihydroergotamine having been conducted in 1986.[8] A summary of the current standard-of-care options and their evidentiary basis is presented in table 1.

The pathological role of calcitonin gene-related peptide (CGRP) in migraine and efficacy of its inhibition in both acute and preventative treatment is well established, and the medications have a favourable side effect profile.[9 10] Eptinezumab achieves maximal plasma concentration immediately following intravenous administration, and once systemically available, may improve migraine from day one. In a recent randomised trial, eptinezumab was superior to placebo in the treatment of an acute migraine attack.[11] With a half-life of 27 days, it continues to exert an effect for a significant period of time.[12 13] Given the immediacy and prolonged efficacy, eptinezumab is likely to be efficacious in the treatment of status migrainosus.

In designing this trial, several considerations have been made. First, the authors considered that a placebo-controlled trial without an active comparator did not represent best practice in the treatment of a prolonged, painful condition. Second, there exists good evidence for the treatment of acute migraine in the ED, however, poor evidence for second-line agents in hospitalised patients when this has failed. Finally, while anaesthetic agents are currently routinely used clinically, they have several drawbacks including potentially prolonged admission and potential cardiac side effects. The study was designed therefore, to not only provide the first high-quality evidence for eptinezumab as a second-line treatment for status migrainosus, but also demonstrate its efficacy in comparison to an active treatment.

Table 1 Inpatient treatment of migraine[7]

Therapeutic option	Strength of evidence
Subcutaneous sumatriptan	Strong recommendation, moderate-quality evidence
Intravenous prochlorperazine	Strong recommendation, high-quality evidence
Intravenous chlorpromazine	Weak recommendation, moderate-quality evidence
Oral NSAIDs	Strong recommendation, low-quality evidence
Intravenous lignocaine	Low-quality evidence,[5 14]
Intravenous ketamine	Low-quality evidence[15]

Given the lack of substantive evidence of current inpatient therapy, the significant potential side effect profile and health-economic cost both in prolonged hospital admission and representation there is an urgent need for new therapies.
NSAID, Non-steroidal anti-inflammatory drug.

OBJECTIVES

Study hypothesis

The primary clinical hypothesis of this study is that treatment with eptinezumab is non-inferior to current standard clinical care (intravenous lignocaine (lidocaine)) in aborting status migrainosus, in patients who have failed or are inappropriate for triptan and intravenous chlorpromazine therapy. The secondary clinical hypothesis is that treatment with eptinezumab will reduce inpatient length of stay, healthcare utilisation at 3 months, and improve patient reported outcome scales related to their migraine disability.

Study objectives

Primary objective

The primary objective of this study is to evaluate the effect of eptinezumab compare to intravenous lignocaine in aborting status migrainosus.

Secondary objectives

This study has several secondary objectives, including:

- To explore the effect of eptinezumab compared with lignocaine on the change from baseline in health resource utilisation.
- To evaluate the effect of eptinezumab compared with intravenous lignocaine on patient-reported outcomes of migraine related disability.
- To evaluate the safety and tolerability of eptinezumab in subjects with status migrainosus.

METHODS AND ANALYSIS

Trial design and study setting

Status migrainosus inpatient treatment with eptinezumab (SMITE) is a randomised, controlled, single-centre clinical trial conducted in a parallel design with an active comparator. This trial involves patients from the Alfred Hospital, Melbourne, Australia, a tertiary academic hospital, who have been admitted under the neurology team in treatment of status migrainosus. The protocol described in this article is version 1.0 of the SMITE protocol, approved on 26 August 2021 by the local Human Research Ethics Committee (HREC) (443/21) and has been registered with the therapeutic goods administration (CT-2021-CTN-03 851-1), and Australia and New Zealand Clinical Trial Registry (ACTRN12621001616864).

Eligibility criteria

Participants who have admitted under the neurology unit of the Alfred Hospital will be eligible to be included if they fulfil the following inclusion and exclusion criteria:

Inclusion criteria

- Aged 18–65 inclusive at time of presentation to ED.

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- At least a 1-year history of migraine with or without aura as per the International Classification of Headache Disorders, third edition (ICHD-3) criteria.
- Age of participant at the time of migraine onset <50 years old.
- An acute migraine attack that has persisted for ≥72 hours as per the ICHD-3 criteria for status migrainosus.
- Ongoing symptoms despite, or contraindication to, triptan and chlorpromazine therapy.
- In the opinion of the investigator and treating doctor, adequate investigation and consideration has been given for secondary causes of headache prior to enrolment.
- Written informed consent obtained from the participant prior to any study-related procedures (online supplemental file 1).

Exclusion criteria

- History of hemiplegic migraine, cluster headache or other trigeminal autonomic cephalalgia.
- Current concomitant diagnosis of a secondary type of headache.
- Chronic headache with continuous pain lasting more than 3 weeks.
- Headache, which in the opinion of the investigator or delegate requires further investigation for secondary causes of headache.
- Any clinically significant haematological, endocrine, pulmonary, hepatic, gastrointestinal or neurological disease.
- Received an anti-CGRP product within 6 months.
- History of known hepatic disease with potential for hepatic function impairment.
- History of myocardial infarction, stroke, transient ischaemic attack, unstable angina or revascularisation procedure.
- Cardiac arrhythmia.
- Newly diagnosed or uncontrolled hypertension.
- Currently received treatment for another investigational drug or within five half-lives since ending treatment of another investigational drug.
- Clinically significant confounding pain disorder.
- Uncontrolled or untreated major psychiatric condition.
- Body mass index >39 kg/m^2.
- Women who are pregnant, breast feeding or planning to become pregnant during the study.
- Previous adverse drug reaction to lignocaine or other local anaesthetics.
- History of malignancy (other than non-melanoma skin cancer, fully treated by excision).
- Previously received intravenous lignocaine for status migrainosus.
- Need for contraindicated proarrhythmic or QT prolonging medication contraindicating lignocaine infusion.

EXPERIMENTAL DESIGN

Interventions

This study was registered on 26 November 2021, and at the time of submission, has not commenced recruitment. It is anticipated to recruit for a twelve month period from January 2021 to January 2022. A complete schedule of activities is presented in table 2. The patient will have baseline data collected (see below), and undergo randomisation.

On randomisation, forty subjects will be allocated in a 1:1 ratio (figure 1) to receive either eptinezumab 300 mg or placebo infusion, and admitted to hospital to receive intravenous lignocaine following local guidelines (online supplemental file 2) as standard medical therapy (if they received a placebo infusion on randomisation), or a placebo infusion for up to 5 days, or until their migraine is successfully treated.

Patients will remain in hospital for up to 5 days in order to allow the maximum treatment duration of lignocaine infusion, but will be allowed to discharge if they have successfully treated their migraine, as defined as two consecutive Visual Analogue Scales (VAS) ≤2. A phone interview, will be conducted at 30 days, and an in-person follow-up visit will be conducted at 90 days after the administration of the investigational product. A final safety phone-call will occur after 140 days.

Randomisation

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel and the sponsor. Allocation will be determined through the use of a centralised web-based randomisation module, utilising a random number generator in the allocation form. Participants will be randomised in equal numbers to intervention and control arms. A member of the research team not otherwise involved in the study will enter the participants' details into the randomisation system, informing the unblinded research pharmacist of the outcome. All appropriate steps will be taken to maintain the blinding of the research team, statistician and treating clinician, including the use of opaque administration sets.

A subject's allocation will be recorded with the unblinded research pharmacist, and in in a tamper-proof envelope. A subject's treatment assignment will be unblinded in two scenarios. In the first scenario, the subject will be unblinded where the knowledge of the treatment is essential for further management or may potentially impact the safety of the subject.

The second scenario is when a subject remains with an untreated headache at the end of the treatment phase (day 5). At this stage, the subject will be unblinded, in order to allow the treating clinician to guide ongoing management. The ongoing management of the patient at this stage will involve part of their routine clinical care, and not considered part of the clinical trial. The subject will continue to have safety follow-up to 140 days.

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Table 2 Schedule of activities

	Screening	Double-blind treatment period (5 days)					Safety/follow-up period		
	ED/visit 1	Inpatient admission/visit 2					Visit 3	Visit 4	Visit 5
	Day 1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 30	Day 90	Day 140
Informed consent	X								
Review eligibility criteria	X								
Randomisation	X								
Medical history	X								X
Concomitant medications	X								
Physical exam	X							X	
Neurological exam	X								
Vital signs	X							X	
Demographics	X								
Clinical labs review	X	X	X	X	X	X		X	
ECG with interpretation	X								
Perform pregnancy test	X								
VAS assessment		X	X	X	X	X			
Perform Headache QuestionnairesΨ		X						X	
Safety review phone call							X		X

Ψ: headache questionnaires: MIDAS, HIT-6, WPAI, EQ-5D, DASS-21, ESS.
DASS-21, Depression Anxiety Stress Scale; EQ-5D, General Health Status Questionnaire; ESS, Epworth Sleepiness Score; HIT-6, headache impact test; MIDAS, Migraine Disability Scale; VAS, Visual Analogue Scale; WPAI, work productivity and activity impairment.

Concomitant care and interventions

Throughout the study, investigators may prescribe any concomitant medication or treatment deemed necessary to provide adequate supportive care except for QT prolonging agents and pro-arrhythmic agents. These will be recorded in the case report form, and included in a secondary analysis.

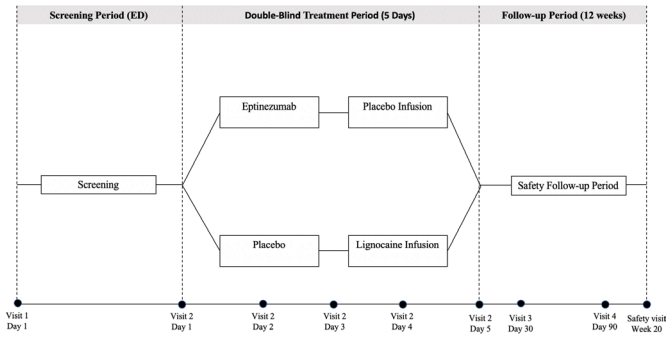

Figure 1 SMITE study schema. ED, emergency department; SMITE, Status migrainosus inpatient treatment with eptinezumab.

Criteria for modifying allocated interventions

No dose modification of the investigational drug is allowed as part of the study. The non-investigational medication may be modified at the treating clinician's discretion to patient tolerability, in keeping with current clinical practice (see online supplemental file 2).

Data collection and management

At the time of enrolment, we will record baseline demographic data, a complete medical and headache history, physical examination, baseline ECG and pregnancy and routine blood tests, as well as baseline efficacy data. While admitted in hospital, patients will undergo efficacy and safety assessments as outlined below. Patients will then be contacted at day 30, 90 and 140 for safety and efficacy follow-up. Data will be recorded in a secure hospital server, with range and validity checks for data values, and double data entry.

Efficacy data

In addition to 3 hourly VAS scores while awake, patients will undergo the following assessment:

- Date and time of start of current migraine.
- Date and time of resolution of current migraine (defined as two consecutive VAS ≤2).

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- Date and time of admission, interventional product infusion and discharge from hospital.
- Baseline monthly number of primary healthcare provider and ED visits for migraine.
- Monthly number of primary healthcare provider and ED visits for migraine at 90 days.
- Baseline score of Migraine Disability Scale (MIDAS), Headache impact test (HIT-6), work productivity and activity impairment (WPAI) and General Health Status (EQ-5D) questionnaires.
- Score of MIDAS, HIT-6, WPAI and EQ-5D at day 90.

Safety data

As part of the routine safety assessment of patients receiving lignocaine infusion in hospital, all patients will receive 4 hourly vital sign observation and daily ECGs and blood tests to assess for electrolyte abnormalities while admitted.

All adverse events will be collected until 90 days after the last dose of the study regardless of whether or not the participant received the study intervention, and as observed or reported by study participants. Care will be taken not to introduce bias when detecting adverse events by using open-ended non-leading verbal questioning of the participant.

Outcomes

The primary endpoint for the study will be the time from infusion initiation to discharge. A number of secondary endpoints will be explored in order to meet the objectives of the study, summarised in table 3. The primary endpoint of the study, time to symptom resolution has been chosen both as a marker of the efficacy of eptinezumab, and to demonstrate the health-economic and patient-centred outcomes of duration of symptoms (and consequently burden of length of stay in hospital).

Participant timeline

The total participant timeline is presented in the schedule of activities (table 2). This incorporates hospital admission for up to 5 days post enrolment, secondary endpoints at 90 days and safety-follow up data to 140 days.

Patient and public involvement

Members of the public or patients were not involved in the study design.

STATISTICAL CONSIDERATIONS

Statistical hypothesis

As this is a non-inferiority study, the primary null hypothesis is that the efficacy of eptinezumab 300 mg intravenous infusion measured in hazard rate of discharge is equal to or worse than non-inferiority margin to intravenous lignocaine in treating status migrainosus. The alternative hypothesis is that the efficacy of eptinezumab 300 mg intravenous infusion compare to intravenous lignocaine in treating status migrainosus is higher than the non-inferiority margin.

- H0: $b \leq \delta$ (Inferior).
- H1: $b > \delta$ (non-inferior).

Table 3 SMITE study objectives and end-points

Objectives	Endpoints
To evaluate the effect of eptinezumab compared with intravenous lignocaine in aborting status migrainosus	► Time from infusion to discharge (Primary outcome) ► Duration of symptoms post infusion ► Visual Analogue Scale (VAS) on discharge or at day five (primary outcome) ► Change in VAS from admission to discharge (primary outcome) ► Use of rescue therapies during the 5-day admission (primary outcome) ► Pain freedom at 2 hours (secondary outcome) ► Freedom from most bothersome symptom at 2 hours (secondary outcome) ► Sustained pain freedom at 24 hours postinfusion in patients who achieve pain freedom (secondary outcome)
To explore the effect of eptinezumab compared with lignocaine on the change from baseline in health resource utilisation	► Change from baseline in monthly number of primary healthcare provider visits (secondary outcome) ► Change from baseline in monthly emergency department visits (secondary outcome)
To evaluate the effect of eptinezumab compared with intravenous lignocaine on patient reported outcomes of migraine related disability	► Change from baseline in MIDAS (secondary outcome) ► Change from baseline HIT-6 (secondary outcome) ► Change from baseline in WPAI (secondary outcome) ► Change from baseline in EQ-5D (secondary outcome)
To evaluate the safety and tolerability of eptinezumab in subjects with status migrainosus	► Adverse events (other safety outcome) ► Clinical laboratory values and vital signs (secondary outcome)

EQ-5D, General Health Status Questionnaire; HIT6, headache impact test; MIDAS, Migraine Disability Scale; SMITE, Status migrainosus inpatient treatment with eptinezumab; WAPI, work productivity and activity impairment.

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Where b is the coefficient equivalent to the log-HR and δ is the non-inferiority margin and <0.

For efficacy analyses, data will be analysed according to participants' randomisation assignments, according to an intention to treat analysis. For safety data analyses, the participants will be analysed according to actual treatment received.

Sample size

There is a paucity of high-quality clinical data on the efficacy of either the experimental or control group in the treatment of status migrainosus, with the largest case series of lignocaine including only five patients with status migrainosus. As such a study of 40 (forty) patients total is proposed. Using one-sided significance level of 0.025, for the primary outcome, the sample size will provide 80% power for a non-inferiority margin of δ=−0.89 or HR of 0.41, that is, the hazard rate of discharge in the eptinezumab group is 41% or lower of the lignocaine group, in univariable Cox regression.

In subsequent secondary multivariable analysis, adjustment for potential risk factors associated with treatment outcome, that is, baseline headache frequency and composite risk score, will be considered. These factors are conservatively assumed to have moderate to strong association (R^2=0.5) with the treatment group, so 50% of the variance of the primary predictor is explained by these factors. We estimate to have 80% power for a non-inferiority margin of δ=−1.25 or HR=0.29 in multivariable Cox regression after adjustment for these factors. Given the short treatment period, we anticipate there will be no drop-outs during the treatment phase.

Statistical analysis

Data analysis will be blinded. The efficacy analyses will be based on an intention to treat analysis. The primary efficacy outcome, time to discharge, will be summarised using median and IQRs as it is anticipated to be non-normally distributed. Univariable Cox regression will be used to estimate the HR of discharge between the eptinezumab and lignocaine groups and its 95% CI will be reported which corresponds to a one-sided significance level of 0.025. If the upper limit of the 95% CI is lower than the non-inferiority margin of HR=0.41, this would indicate eptinezumab has an unacceptably worse efficacy than lignocaine. Non-inferiority p value will also be calculated. Multivariable Cox regression with adjustment of baseline headache frequency and composite risk score as subsequent secondary analysis will be performed.

For secondary efficacy and follow-up outcomes, continuous variables will be summarised using means and SD or medians and IQRs depending on the underlying data distribution. Categorical variables will be expressed as counts and proportions. Exploratory univariable analysis will be conducted using Student's t-test, Mann-Whitney U test,χ^2 or Fisher's exact tests where appropriate.

Safety and tolerability outcomes, such as adverse events, will be descriptively summarised.

All statistical tests will be performed by using statistical software packages R (R Core Team), Stata (StataCorp) or SPSS (IBM).

Auditing

An annual audit detailing recruitment, adverse events and complaints will be performed and submitted to the local HREC, in compliance with local policies. This will be performed by the principal investigator. An interim analysis will not be performed due to the small sample size and projected length of the study.

ETHICS AND DISSEMINATION

Research ethics approval and consent

This study will be conducted in accordance with the ICH note for guidance on Good Clinical Practice (GCP) and has been reviewed and approved by the Human Research Ethics Committee of Alfred Health (local reference number 443/21). Informed consent will be obtained from potential participants by a senior doctor in the trial team, who has GCP certification and is registered with the local HREC, for participation in the trial and dissemination of trial results. The consent form is included as online supplemental file 1.

Confidentiality and dissemination

Personal information will be stored in a study database on a secured hospital server, accessible only to the study team. Results will occur only in a deidentified, grouped manner to reduce the risk of identification of participants. The results will be actively disseminated through peer-reviewed journals, conference presentations and social media.

Data sharing

Requests for deidentified individual data, and the study protocol can be made between 3 months and 5 years following publication by researchers with a methodologically sound proposal. Requests can be made by arrangement with the corresponding author via j.ray@alfred.org.au.

DISCUSSION

Strengths and limitations of the SMITE trial design

This study is the first randomised controlled study to evaluate the use of eptinezumab in the treatment of status migrainosus. Its design, in comparing eptinezumab to existing standard treatment, will provide clinically a meaningful outcome for clinicians. In addition, it incorporates both patient-centred and health-economic outcomes to provide a greater context of the efficacy of the trial medication.

There are several potential limitations to this study design. As a single-site study, the generalisability of the results to diverse patient populations will require careful consideration. The allowance of concomitant medications during the trial period may have the effect of diluting the

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treatment difference between patient groups, however, was felt to be important ethically in patients hospitalised for a painful condition by the investigators. The paucity of high-quality data on the efficacy of lignocaine also limits the power analysis. Finally, this study will be undertaken in the midst of the COVID-19 pandemic. It is likely that hospital resources will be stretched, and hospital presentations for non-respiratory illnesses will be reduced. It is anticipated that this may cause slower recruitment then projected, however, should not interfere with the study.

Twitter Jason Charles Ray @dr_jray1 and Elspeth J Hutton @spiraldance1

Authors contributions JCR and EJH conceptualised the project and developed the protocol with the assistance of JG and GR. ZC provided additional expertise in the statistical analysis. JCR drafted the manuscript and all authors reviewed and edited the manuscript.

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Competing interests JCR has received compensation from the Pharmaceutical Society of Australia, sponsored by Viatris for educational material. ZC is supported by an Early Career Fellowship from the National Health and Medical Research Council (NHMRC) of Australia (GNT1156444). He/his institution has received consultancy fees and/or research grants from Arvelle Therapeutics and UCB Pharma for works outside the submitted work. EJH has served on advisory boards for Sanofi-Genzyme, Novartis, Teva, Eli Lilly, Allergan, Lundbeck, been involved in clinical trials sponsored by Novartis, Teva, Xalud, Daewong and Novotech, and has received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD

Jason Charles Ray http://orcid.org/0000-0003-4833-5507

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Alfred Health

Title	An evaluation of the efficacy of eptinezumab in the inpatient management of status migrainosus in comparison to intravenous lignocaine in patients who have failed other therapies
Short Title	SMITE: Status Migrainosus Inpatient Treatment with Eptinezumab
Protocol Number	1.0
Project Sponsor	Alfred Health
Principal Investigator	Dr. Jason Ray/Dr. Elspeth Hutton
Associate Investigator(s)	Dr. Mahima Kapoor Dr Emma Foster
HREC Reference	HREC/77323/Alfred-2021
Location	The Alfred Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you are currently suffering from a migraine, and have presented to hospital with status migrainosus (a migraine attack that has lasted more than three days). The research project is testing a new treatment for status migrainosus. The new treatment is called eptinezumab.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your treating doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project

• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of this study is to determine the safety and efficacy of eptinezumab in treating status migrainosus, compared to usual treatment for this condition (intravenous lignocaine). Currently, there are only limited options in treating status migrainosus, and no high-quality research into its treatment. This study will provide doctors with evidence on how to best treat patients who present to hospital with status migrainosus in the future.

Eptinezumab is an intravenous medication which targets calcitonin gene-related peptide (CGRP). Eptinezumab is approved by the Therapeutic Goods Administration (TGA) for the prevention of migraine, and has been shown in clinical trials to reduce the frequency of migraine attacks. It has not previously been studied to see if it stops an acute attack of status migrainosus in migraine patients. Therefore, it is an experimental treatment for status migrainosus. This means that it must be tested to see if it is an effective treatment. It is an infusion which takes 30 minutes. The most commonly reported side effects are nasopharyngitis (cold-like symptoms) (8%) or sensitivity reactions (flushing, hot flush, itching, allergic reaction) in 2% of people.

Lignocaine is an intravenous medication which is currently used as the standard care in treating status migrainosus. It is an anaesthetic medication which is given for up to five days to treat status migrainosus.

This research has been initiated by the study doctors, Dr Elspeth Hutton and Dr Jason Ray. It has received funding from Lundbeck Australia Pty Ltd, the company that produces eptinezumab.

3 What does participation in this research involve?

You will be invited to participate in this research if you are between the ages of 18 and 65, have a diagnosis of migraine for more than one year, and are admitted to hospital for treatment of status migrainosus that has not responded to, or have a contraindication to, standard treatment (triptans and chlorpromazine). You will be given this information to read, and have time to answer any questions you may have related to the trial. If you agree to participate, you will be asked to sign the consent form prior to any study assessments being performed.

If you consent, you will be participating in a randomised controlled clinical trial. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). This is a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.

Screening

Initially, you will undergo screening with the study doctor to ensure that you are eligible for the study. This is to ensure that this is an appropriate study for you, and that you do not have a condition that would make either treatment unsafe. This will involve:

- Asking questions related to your medical history and presentation to hospital,
- A physical examination, (including height and weight)
- Undergoing blood tests, including a pregnancy test (if applicable)
- Having an electrocardiogram (ECG).

After screening, you will be randomised to receive one of two treatments.

Study Procedures

You will receive either:

- A 30-minute intravenous infusion of 300mg of eptinezumab (the trial medication) followed by up to five days of a placebo intravenous infusion

OR

- A 30-minute placebo intravenous infusion, followed by up to five days of a lignocaine intravenous infusion (the current standard treatment, 2mg/min)

Throughout the study, you will be able to receive other pain relief medication if required.

A placebo is a medication with no active ingredients or a procedure without any medical benefit. It looks like the real thing but is not. This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way.

On the first day of treatment, you will also be asked to complete four (4) questionnaires on the effect that migraine has on your life, this takes approximately 15 minutes to complete. While you are in hospital receiving the five-day infusions we will:

- Perform daily blood tests (including full blood count, kidney function, electrolytes, magnesium and liver function) and daily ECGs
- Ask you to rate your pain scale on a scale from 1-10 every three hours while you are awake
- We will document your medical history, vital signs, and physical examination throughout your admission

You will be discharged from hospital after five days, or once your pain score has reduced to less than two on two consecutive occasions, whichever occurs first. If after the five-day infusion you still have ongoing pain, your ongoing care will be determined by your treating doctor. You will be asked to keep a headache diary for the next 3 months, and asked to record how many times you present to either your local doctor or an emergency department for your migraine.

You will be contacted by the study doctor by phone 30 (thirty) days after going to hospital to check whether you have any adverse events, how often you saw a doctor for your migraine, and how many migraines you have had. You will then have a final visit after 90 (ninety) days to complete the same four surveys you did in hospital, and assess your migraine frequency. You will have a final phone call 20 (twenty) weeks after your first visit to hospital to ensure that you have not developed any side effects of the treatment.

Your involvement in this research project will be the length of your hospital admission for status migrainosus (up to five days), two phone calls and then one study visit, over a total of 20 weeks. There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge. You will be reimbursed for any reasonable travel, parking, meals and other expenses associated with the research project visits.

If you decide to participate in this research project, the study doctor will inform your local doctor.

4 What do I have to do?

If you agree to take part in this study, you will receive medication to treat status migrainosus. You will not need to stay in hospital longer then is required to treat your pain. While in hospital, your doctors will continue your regular medication, which will be given by the nursing staff as usual.

You should not donate blood or fall pregnant for six months after participating in this study. There are no other lifestyle restrictions from participation in this study. It is important that you continue a headache diary and complete the follow-up reviews after you leave hospital. There will be two phone calls scheduled to discuss your health and collect information about any potential side effects from the treatment you received during the trial. There will be one in-person study visit when safety assessments will be conducted.

5 Other relevant information about the research project

This study is being undertaken at the Alfred Hospital. A total of forty people will take part in this study, and divided randomly and equally into two groups:

- Twenty people will receive eptinezumab and then a placebo infusion for up to five days
- Twenty people will receive a placebo infusion and then a lignocaine infusion for up to five days

This study is the first of its kind to assess either the treatment of status migrainosus in a controlled manner, or the use of eptinezumab as a treatment of status migrainosus.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Alfred Health.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include intravenous lignocaine infusion, the standard treatment for status migranosus. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your treating doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include:

- Treatment of your current presentation with status migrainosus
- A reduced length in hospital
- Fewer migraine days in the next three months

9 What are the possible risks and disadvantages of taking part?

9.1 Possible side effects

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Having a drug injected or blood taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

Possible side effects of eptinezumab include:

Side Effect	How often is it likely to occur?	How severe might it be?	How long might it last?
Nasopharyngitis	Eight in every hundred patients	Mild	A couple of days
Hypersensitivity reaction*	two in every hundred patients	Mild	During infusion

* hypersensitivity reactions included itching, flushing, or allergic reaction on the day of infusion

9.2 Issues relating to pregnancy, breast-feeding or planned parenthood

The effects of eptinezumab on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least six months after the last dose of study medication.
Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of six months after enrolment in the research project. You should discuss methods of effective contraception with your study doctor.

If you do become pregnant or father a child whilst participating in the research project, you should advise your study doctor immediately.
Your study doctor will advise on medical attention for you or your partner should this be necessary. In the event you become pregnant or father a child during the course of this study, the study sponsor would like to collect information on your/your partner's pregnancy and its outcome. You will be provided with a separate Participant Information Sheet/Consent Form to read and consider.

9.3 Psychological distress

If you become upset or distressed as a result of your participation in this project, or as a result of completing the questionnaires the researchers will be able to help arrange appropriate support. We anticipate that any symptoms of distress or anxiety will be addressed by your clinician in the consultation, and we will guide you to appropriate resources for further evaluation or treatment as needed.

10 What will happen to my test samples?

You will be asked to provide additional consent for the collection of your blood during the research project. This is a necessary part of the project to ensure the safety of your clinical care.

Samples of your blood obtained for the purpose of this research project will be processed at Alfred Health. Your blood will only be used for tests that directly relate to your clinical care, and not for any other research purpose.

If we detect a significant or abnormal test result, we will inform you as part of your routine clinical care.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

During this research project you would not be able to start a new (or different) medication which is designed to reduce the frequency of migraine attacks.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. If you withdraw from the project, you will be invited to continue to attend the follow up visits. This is to ensure that we have as much information about the safety of the medication as possible.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by Alfred Health up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug/treatment/device being shown not to be effective
• The drug/treatment/device being shown to work and not need further testing
• Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

15 What happens when the research project ends?

Following the end of your participation in the study, you will be invited to attend and continue to follow-up the management of migraine at the headache clinic of Alfred Health. Eptinezumab is not available on the pharmaceutical benefit scheme, so you would not be able to continue the medication after the end of the trial, however the clinic specialists will be able to discuss with you other options in managing your migraine.

The results of the study will be published following its conclusion in a peer-reviewed medical journal. We would be happy to write you a letter sharing a summary of the results of the study with you once it has been completed. This will include information about the overall results of the study, not specific information about your individual results. If you would like to receive a copy of the results, please indicate below:

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. It will be treated as all other confidential medical information, stored on a secure REDCap password protected server at Alfred Health. Only researchers involved in the study will be able to access this information. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this health service for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, Alfred Health, the institution relevant to this Participant Information Sheet, Alfred Health, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Results will only be presented in a non-identifiable, generalised form.

Information about your participation in this research project may be recorded in your health records. In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is being conducted by Dr. Elspeth Hutton and Dr. Jason Ray, and sponsored by Alfred Health. This study is being conducted with the support of Lundbeck Australia Pty Ltd, a company that produces eptinezumab under the trademark Vyepti.

Lundbeck may benefit financially from this research project if, for example, the project assists Lundbeck to obtain approval for a new indication for eptinezumab.

You will not benefit financially from your involvement in this research project..

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Lundbeck, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Alfred Health will receive a payment from Lundbeck for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

Dr. Hutton has received an honorarium for sitting on the Lundbeck medical advisory board. No other members of the research team have declarations of interest.

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Alfred Health, the institution where both the research and standard care will be carried out.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 03 9074 2470 or any of the following people:

Clinical contact person

Name	Georgia Ramsay
Position	Study Coordinator
Telephone	03 9074 2470
Email	g.ramsay@alfred.org.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Position	Complaints Officer
Telephone	03 90763619
Email	research@alfred.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Local HREC Office contact (Single Site - Research Governance Officer)

Name	Alfred Health HREC
Position	HREC Executive Officer
Telephone	03 9076 3618
Email	research@alfred.org.au

AH 443.21

Consent Form - *Adult providing own consent*

Title	An evaluation of the efficacy of eptinezumab in the inpatient management of status migrainosus in comparison to intravenous lignocaine in patients who have failed other therapies
Short Title	SMITE: Status Migrainosus Inpatient Treatment with Eptinezumab
Protocol Number	1.0
Project Sponsor	Alfred Health
Coordinating Principal Investigator/ Principal Investigator	Dr. Jason Ray/Dr. Elspeth Hutton
Associate Investigator(s)	Dr. Mahima Kapoor Dr. Emma Foster
HREC Reference	HREC/77323/Alfred-2021
Location	The Alfred Hospital

Consent Agreement

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Alfred Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I would like to receive a summary of the research results. ☐ Yes ☐ No

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Declaration - for participants unable to read the information and consent form
Witness to the informed consent process
Name (please print) _____

Signature _____ Date _____
* Witness is not to be the Investigator, a member of the study team or their delegate. Witness must be 18 years or older.

AH 443.21

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Name of Participant (please print) _____

Signature _____ Date _____

For participants unable to read the information and consent form
Witness to the informed consent process
Name (please print) _____
Signature _____ Date _____
* Witness is not to be the Investigator, a member of the study team or their delegate. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

AH 443.21

Form for Withdrawal of Participation - *Adult providing own consent*

Title	An evaluation of the efficacy of eptinezumab in the inpatient management of status migrainosus in comparison to intravenous lignocaine in patients who have failed other therapies
Short Title	SMITE: Status Migrainosus Inpatient Treatment with Eptinezumab
Protocol Number	1.0
Project Sponsor	Alfred Health
Coordinating Principal Investigator/ Principal Investigator	Dr. Jason Ray/Dr. Elspeth Hutton
Associate Investigator(s)	Dr. Mahima Kapoor Dr. Emma Foster
HREC Reference	HREC/77323/Alfred-2021
Location	The Alfred Hospital

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Alfred Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

DRUG GUIDELINE

AlfredHealth

Title LIGNOCAINE INFUSION FOR NEUROPATHIC PAIN

This drug guideline has been prepared to standardise the prescribing, administration and dispensing of this specific medication. Additional information relating to this drug can be found in the references listed and by contacting the Alfred Medicines Information Service on 62002.

Areas Applicable: Alfred– All Areas under the direction of Palliative Care and Acute Pain Services

Description	
Drug Presentation	• Lignocaine 500 mg in 5 mL (**Xylocard® 10%**) • **Note: Some lignocaine products also contain adrenaline, check carefully that the correct strength & product has been selected**
Prescribing Requirements /Restrictions	• Use for neuropathic pain treatment or pain relief in burns must be initiated by Acute Pain Services (APS) or Palliative Care Unit.
Drug Storage/ Availability	• Store ampoules below 25 degrees C.
Action (Pharmacology)	Lignocaine is an amide local anaesthetic which produces analgesia by blockade of peripheral and central sodium ion channels. The prevention of sodium influx will inhibit propagation of action potential to block pain conduction by nerves. Lignocaine has been used for the following indications: • Neuropathic pain. • Chronic daily headache in patients with rebound headache / migraine (see Lignocaine infusion for analgesic rebound headache/migraine) • Class 1B cardiac anti-arrhythmic agent for serious ventricular arrhythmias (see 'Lignocaine Infusion for Arrhythmias') • Half- life for infusion is 1.5 to 2 hours; this will be extended in patients with hepatic and/or heart failure. During continuous infusion, steady state is reached after 6 to 8 hours

Indications	To be prescribed by either Acute Pain Services or Palliative Care Unit for the treatment of:
	• Neuropathic pain when standard therapies do not provide adequate pain relief
	• Pain relief in burns patients (under the direction of Acute Pain Services) –
	  ○ Used perioperatively for the treatment of donor site pain.
	  ○ Where anti-neuropathic options have already been optimised.
	  ○ Considered for burns patients whose background opioids are ≥150mg/day MOE (Morphine Oral Equivalent)
	• Lignocaine infusion can be commenced ONE hour prior to dressing change and continue for ONE hour post dressing change (see 'ICU Management of Procedural Pain for Intubated Burn Patients')
	• For treatment of serious arrhythmias – see 'Lignocaine Infusion for Arrhythmia'

Contraindications	• Patients with sinoatrial or atrioventricular (especially 2nd or 3rd degree) blocks or intraventricular blocks or other conduction defects on 12-lead ECG (unless pacemaker in situ). *Note: A patient with pre-existing **first** degree heart block may receive lignocaine infusions only after obtaining agreement from the Cardiology Unit.* • Pre-existing hypotension (especially if symptomatic)

The hard copy of this document may be out of date. To ensure you are reading the current version, check the policy and procedure site on the Alfred Health Intranet.

DRUG GUIDELINE

AlfredHealth

Title LIGNOCAINE INFUSION FOR NEUROPATHIC PAIN

Contraindications Continued	• Bradycardia • Supraventricular tachycardia e.g. AF • Cardiac failure • Uncontrolled epilepsy • Known hypersensitivity to amide local anaesthetic agents such as prilocaine & bupivacaine (rare)
Precautions	• Possible to induce tachycardia via re-entry mechanism e.g. in Wolff-Parkinson-White Syndrome • The infusion should be ceased immediately if patient experiences serious cardiac or respiratory or neurological side effects. Notify medical staff for an urgent review • Postural orthostatic tachycardia syndrome (POTS) – bed rest may exacerbate this condition. Please discuss with the treating cardiologist prior to admission. • Beware of polypharmacy, particularly with agents which may prolong QTc (see Drug interactions). • Lower dose in elderly patients and in those with (see Dose range) – Body weight < 80kg – Obesity (>120kg) – heart failure – liver failure – consider halving the dose in those with severe impairment and continuous cardiac monitoring – renal failure (renal impairment is unlikely to affect lignocaine clearance if duration is < 24 hrs, however, toxicity may still develop after prolonged use with accumulation of a less active metabolite).
Administration	
Pre-treatment requirements	A thorough medical assessment/ examination is required before starting infusion (refer to 'Contraindications' section) • A baseline 12 lead ECG (Chest burns where a 12 lead ECG is unable to be obtained then a 3 Lead ECG will be adequate) • LFT, FBC, U&E, Calcium, Magnesium, Phosphate. • Baseline vital signs - BP, pulse, respiratory rate and temperature **Resuscitation equipment** must be made available prior to administration **These may not be required in palliative patients at the discretion of the Palliative Care Unit.**
Dose Range	**Usual Dose** • 25 mL/hour = 2 mg /min (unless otherwise specified by the Consultant in charge or meets criteria for a lower dose). The maximum dose is 2.4 mg/min, • Consider lower dose (i.e. 12.5 mL/hour) in the following patients: ○ body weight < 80kg ○ the elderly > 75 years ○ heart failure, ○ shock ○ liver impairment; ○ renal impairment NOTE there is a separate dose regime for subcutaneous infusion see below.

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DRUG GUIDELINE

AlfredHealth

Title LIGNOCAINE INFUSION FOR NEUROPATHIC PAIN

	Must first ascertain whether patient requires continuous cardiac monitoring. The decision to initiate prolonged lignocaine infusions if continuous cardiac monitoring is required can be made by the Palliative Care or Acute Pain Service only after obtaining agreement from the Cardiology Unit. Patients who require monitoring will be transferred to a ward with monitored beds. Continuous cardiac monitoring is required in: 1. Patients with pre-existing first degree heart block prior to lignocaine administration AND the Cardiology Unit has specifically requested continuous cardiac monitoring. (Note*: Lignocaine is contraindicated in patients with* 2nd or 3rd *degree heart blocks*) 2. Patients in whom the prescribed lignocaine dose is **>2 mg/min**. However, an exception for the need to have continuous cardiac monitoring can be made for ○ patients who weigh >70 kg with no cardiac complications, and ○ in whom the lower dose of ≤2 mg/ min has proven to be ineffective. In these patients, the Palliative Care or APS Consultant may specifically increase the dose up the maximum allowable dose of 2.4 mg/min without requiring continuous cardiac monitoring Check fluid and electrolyte status. **Ensure normal K+ level** before starting treatment as both hypo- or hyperkalaemia can increase risk of arrhythmia. **Resuscitation equipment** must be made available prior to administration For patients who do not require continuous cardiac monitoring, refer to "Monitoring".
Intravenous Infusion	Infusion Concentration: 2400 mg Lignocaine (= 24 mL of 500 mg/5 mL amp) Make up infusion in: 500 mL bag Compatible Solutions: 0.9% sodium chloride Volume to be removed: Nil Final Concentration: 4.8 mg/mL* Usual Dose 2 mg/min (= 25mL) – see dose range Infusion pump: Continuous infusion pump e,g Carefusion Alaris ** These concentrations do not take into consideration the additional added volume. Additional volume is only calculated for when it exceeds 10% of the total volume*
Subcutaneous Infusion via NIKI T34 syringe driver	The Niki T34 pump: Prescription must be written on a subcutaneous prescription chart MR M67 (see Niki T34 guideline) Infusion Concentration: Commence at 500 mg Lignocaine/24 hours If pain inadequately controlled after 6 hours consider titration in increments of 250-500mg to maximum of 2500mg per 24 hours Make up infusion in: 20mL Luer Lok syringe Compatible Solutions: 0.9% sodium chloride to a total volume of 15mLs **For doses greater than 1500mg (15mLs) the dose should be split and run via two Niki T34 infusion pumps simultaneously**

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DRUG GUIDELINE

AlfredHealth

Title LIGNOCAINE INFUSION FOR NEUROPATHIC PAIN

Titration Parameters	• Not titrated - infused as ordered by Acute Pain Services / Palliative Care Unit
How to wean infusion/dose	• The lignocaine infusion can be ceased abruptly without titrating down
Incompatibilities	• Refer to Australian Injectable Drugs Handbook
Y-Site Compatibility	• A secondary infusion/injection should not be delivered through the same line as the lignocaine Infusion, unless in case of emergency, as the patient is at risk of receiving a bolus of lignocaine.
pH	• 5 – 7
Practice Points	
Side Effects	*Adverse effects are dose-related and occur more frequently at infusion rates ≥ 3 mg/min. Signs of CNS toxicity usually precede those of the cardiovascular system* **Central nervous system:** • Light headedness/ dizziness/ drowsiness/ restlessness/ confusion • Nausea & vomiting • Perioral tingling or tongue numbness • Twitching/ tremor/ paraesthesia • Seizure/ convulsion • Visual disturbances/ blurred vision • Speech disturbances (e.g. slurred speech) • Tinnitus • Euphoria/ hallucinations • Reduced level of consciousness, coma • Respiratory arrest **Cardiovascular system:** • Hypotension • Bradycardia or arrhythmia • AV heart block (new or worsened) or suppression of SA node • May promote tachycardia via re-entry mechanism • Asystole • May decrease effectiveness of DCR Hypersensitivity reactions – occurs rarely e.g. urticaria, rash and anaphylaxis With suspected toxicity a lignocaine toxicity level should be performed (a red top blood tube can be sourced from Main Recovery) as soon as the symptoms are reported

Monitoring IV infusion protocol	*Prior to commencement of infusion*
	• A baseline 12 lead ECG (Chest burns where a 12 lead ECG is unable to be obtained then a 3 Lead ECG will be adequate)
	• Baseline vital signs - BP, pulse, respiratory rate and temperature
	
	After commencing the infusion:
	• BP, heart rate and sedation score:
	  ○ Every hour for 4 hours, then
	  ○ Every 2 hours for 4 hours, then
	  ○ Every 4 hours

DRUG GUIDELINE

AlfredHealth

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	• Pain Score:
	  ○ Every hour for 4 hours, then
	  ○ Every 4hours (omit between 2200 and 0600 if asleep)
	• Daily 12 lead ECG or 3 lead for QTc assessment
	• Paraesthesia:
	  ○ Ask patient to report paraesthesia around mouth immediately
	  ○ Ask about paraesthesia around mouth every 4 hours for first 24hours after initiating lignocaine or adjusting dose
	  ○ Once patient has been on stable dose for 24hours monitoring can be reduce to every 6 hours
	• Toxicity/Signs and symptoms of Overdose:
	  ○ Check for signs of toxicity at least once per shift Document any neurological side effects (even if absent)
	  ○ Escalate to medical staff if signs of toxicity present.
	
	Infusion should be stopped immediately if serious cardiac or neurological or respiratory side effects are suspected.
	If signs/symptoms of above side effects, escalate to medical staff for an urgent review.
	
	If convulsions occur CALL a MET call and immediately inform Acute Pain Service **4732**
	
	Lignocaine levels must be taken – red top blood tubes sourced from Recovery Unit.

Monitoring subcutaneous infusion protocol	Monitoring requirements in palliative care patients to be at the discretion of the Palliative Care Unit. For all other patients monitoring is as follows;
	
	Prior to commencement of infusion
	• A baseline 12 lead ECG (or 3 lead rhythm strip for patients unable to establish 12 lead, ie burns)
	• Baseline vital signs - BP, pulse, respiratory rate and temperature
	
	After commencing the infusion
	(Monitoring requirements may be reduced at the discretion of the palliative care team)
	• BP, heart rate, sedation score:
	  ○ Every hour for 4 hours for first 24hours after initiating lignocaine or adjusting dose
	  ○ Once patient has been on stable dose for 24hours monitoring can be reduced to every 6 hours
	• Pain Score:
	  ○ Every 6 hours (omit between 2200 and 0600 if asleep)
	• Paraesthesia:
	  ○ Ask patient to report paraesthesia around mouth immediately
	  ○ Ask about paraesthesia around mouth every 4 hours for first 24hours after initiating lignocaine or adjusting dose
	  ○ Once patient has been on stable dose for 24hours monitoring can be reduce to every 6 hours
	• Toxicity/Signs and symptoms of Overdose:
	  ○ Check for signs of toxicity at least once per shift and specifically record their absence in the nursing notes

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	○ If present, cease infusion, give supplementary oxygen, and immediately inform Acute Pain Service, or Palliative Care Service Dr. • Daily 12 lead ECG or 3 lead for QTc assessment
Drug Interactions	Lignocaine is primarily metabolised by cytochrome P450 isoenzyme 1A2 in the liver, and to a lesser extent by 3A4 enzymes: *Note: Lignocaine synonym is lidocaine. Use lidocaine to search in databases* • **QT prolonging agents** – Azole antifungals, antipsychotics, some antidepressants e.g. citalopram, antiarrythmics, macrolides, methadone, quinolones & tyrosine kinase inhibitors especially nilotinib. See 2017 list of drugs that prolong QT and/or cause Torsades De Pointes or register for Credible Meds website for up to date information • **Pro-arrhythmic agents** – antiarrhythmics esp. Class III potassium-channel blockers e.g. amiodarone & sotalol, macrolides e.g. clarithromycin, quinolones, azole antifungals and antipsychotics e.g. quetiapine[6,7] • General Interactions – See Stockley online for specific interactions e.g. potent 3A4 inhibitors such as azoles *This list only includes some of the common drugs and is by no means exhaustive. Contact your Clinical Pharmacist or call Medicines Information on 62002 for details relating to individual drugs.*
Use in Pregnancy/Lactation	See The Women's Hospital's online Pregnancy and Breastfeeding Medicines Guide

Key Related Documents

Alfred Health Drug Formulary Guideline

Neurology Resident Orientation Handbook 2016

ICU Management of Procedural Pain for Intubated Burn Patients Guideline

Lignocaine Infusion for Arrhythmia Guideline'

Peripheral Intravenous Cannulation & Ongoing Management Guideline: Adults

Niki T34 Subcutaneous Pump (Syringe Driver) Guideline

Lignocaine Infusion for Analgesic Rebound Headache/Migraine Guideline

Key Legislation, Acts & Standards

Charter of Human Rights and Responsibilities Act 2006 (Vic)[1]

References

1. (2014), *Cochrane Database Syst Rev, 10,* CD005622
2. Ashely C, Currie A. The Renal Drug Handbook. 3rd Edition. Radcliffe Publishing Ltd, U.K. 2009

[1] REMINDER: Charter of Human Rights and Responsibilities Act 2006 – All those involved in decisions based on this guideline have an obligation to ensure that all decisions and actions are compatible with relevant human rights.

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4. Mao J, et al. Systemic lidocaine for neuropathic pain relief. Pain 2000; 87: 7-17
5. Peixoto R, Hawley P. Intravenous lidocaine for cancer pain without electrocardiographic monitoring: a retrospective review. J Palliat Med. 2015 Apr;18(4):373-7.
6. Schwartzman RJ et al. "Efficacy of 5-day continuous lignocaine infusion for the treatment of refractory complex regional pain syndrome" Pain Medicine 2009: 10(2); 401-412
7. Wasiak J, Cleland H Lidocaine for pain relief in burn injured patients(2007), *Cochrane Database Syst Rev, 18;(3),* CD005622 (R)
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10. Williams DR & Stark RJ. Intravenous lignocaine (Lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia 2003: 2; 963-971
11. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Education 2016;16(9):292-298
12. General resources also used in the preparation of this monograph include: *MIMS* [On-Line] (accessed 25/01/10); *Micromedex* [On-Line] (accessed 25/01/10); *Australian Medicines Handbook* [On-line (accessed 25/1/10); Burridge N (ed) *Australian Injectable Drugs Handbook*. 4th Edition. Melbourne: The Society of Hospital Pharmacists of Australia, 2008. *Pregnancy and Breastfeeding Medicines Guide.* Melbourne: The Royal Women's Hospital, 2010.

AUTHOR / CONTRIBUTORS

* denotes key contact

Name	Position	Service / Program
Kerry McLaughlin*	Consultant - APS	Surgical Services
Eliza Bell	Pain Liaison Nurse - APS	Surgical Services
Michelle Gold	Director, Palliative Care	Surgical Services
Cathy Corbett	Consultant, Palliative Care	Surgical Services
Alex Konstantatos	Head of Acute Pain Service, Consultant	Surgical Services
Thuy Bui	Analgesic Stewardship Pharmacist	Pharmacy
John Dalla	Palliative Care Nurse	Cancer & Medical Specialties
Mel Pacquola	Burns Liaison Nurse	Surgical Services
Heather Cleland	Director, Burns Unit	Surgical Services
Hana Menezes	Burns Nurse Practitioner Candidate	Surgical Services
Sarah Larwill	Clinical Services Director, Surgical Services	Surgical Services

Endorsed by:	Name/Title: Prof Michael Dooley – Director, Pharmacy	Date: 13 September 2017
Approved by:	Name/Title: Alfred Health Drug and Therapeutics Committee	Date: 13 September 2017
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