PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Status migrainosus inpatient treatment with eptinezumab (SMITE): Study protocol for a randomised controlled trial
AUTHORS	Ray, Jason; Chen, Zhibin; Ramsay, Georgia; Germaine, Jack; Hutton, Elspeth

VERSION 1 – REVIEW

REVIEWER	Martelletti, Paolo Sapienza University of Rome
REVIEW RETURNED	10-Dec-2021

GENERAL COMMENTS	This manuscript reports a draft protocol for the use of eptinezumab, the only one among monoclonal antibodies approved for the prevention of migraine to be used intravenously every 3 months, not for prevention as recorded but for treatment in emergency departments of status migrainosus. This protocol overturns the positioning of this drug, which in registration studies has shown a very high efficacy with an equal safety profile (as also shown in all pharmacological class to which it belongs) as a prev to migraine prevention agent, leading to hypothesize its possible role (experimental) in the acute phase of migraine, in particular status migrainosus, classifiable as a resistant and refractory migraine. In this regard it is good to suggest to the Authors an interesting fact that the definition of Resistant and Refractory migraine has been codified by the European Headache Federation and should be taken into account (PMID: 32546227). Similarly, it should be reported the data related to the numerical importance of the accesses to the ER with a diagnosis of primary headache (PMID: 31690261). Innovative idea, methodology correctly proposed in this interesting protocol.

REVIEWER	Wang, Zhong First Affiliated Hospital of Soochow University, Department of Neurosurgery
REVIEW RETURNED	20-Dec-2021

GENERAL COMMENTS	This article describes in detail a randomized controlled trial of eptinezumab and intravenous lignocaine for status migrainosus inpatient treatment, with clear logic and clear protocol. It also describes in detail the background, research method, experimental design, statistical analysis and discussion of comparing the treatment effects of the two drugs. But there are still some problems: 1.The title of this article is " Status migrainosus inpatient treatment with eptinezumab (SMITE): Study protocol for a randomised controlled trial", easy to cause misunderstanding, normally should be compared with high-quality evidence treatment, such as triptans and intravenous prochlorperazine or chlorpromazine, or understood as compared with all conventional clinical treatment. The title of the article should be amended to highlight the comparison between Eptinezumab and intravenous lignocaine。 2.The article compared eptinezumab and intravenous lignocaine for status migrainosus inpatient, but there is no high-quality clinical evidence for intravenous lidocaine therapy for migraine itself. Although recommended by guidelines, it is not an accepted clinical treatment for migraine and is usually only attempted if triptans and prochlorazine have failed treatment, with limited clinical applicability. Moreover, i intravenous lignocaine can lead to a series of cardiovascular changes and increase the risk of abnormal heart beats such as atrioventricular block. Therefore, the clinical significance of this study is small. 3.Intravenous infusion eptinezumab 300mg compared with intravenous lidocaine injection for five consecutive days after admission, the first difference is administration is different, and the second difference is the time of receiving the drug. Whether there is an effect on the therapeutic effect, whether eptinezumab needs to be supplemented daily to maintain optimal drug concentration. 4.The article lacks a list of abbreviations. 5.Is it contrary to our common understanding to put a cross on items in table2.

REVIEWER	Scuteri, Damiana University of Calabria
REVIEW RETURNED	23-Dec-2021

GENERAL COMMENTS	General comment The Ms entitled “Status migrainosus inpatient treatment with eptinezumab (SMITE): Study protocol for a randomised controlled trial” is a study protocol to investigate the possible efficacy of eptinezumab in the treatment of status migrainosus often resistant to treatment and leading to hospitalization for its characteristic to achieve maximal plasma concentration immediately following administration and potential to improve migraine pain from the first day of treatment. Major comments The novelty of this study is downgraded by the present previous study: Winner PK, McAllister P, Chakhava G, Ailani J, Ettrup A, Krog Josiassen M, Lindsten A, Mehta L, Cady R. Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most

	Bothersome Symptom When Initiated During a Migraine Attack: A Randomized Clinical Trial. JAMA. 2021 Jun 15;325(23):2348-2356. doi: 10.1001/jama.2021.7665. PMID: 34128999; PMCID: PMC8207242. Accordingly, the Authors do not cite the latter study as well as recent literature suggesting and supporting the role of eptinezumab in the treatment of migraine attacks and status migrainosus as the following Ms: Scuteri D, Bagetta G. Progress in the Treatment of Migraine Attacks: From Traditional Approaches to Eptinezumab. Pharmaceuticals (Basel). 2021 Sep 13;14(9):924. doi: 10.3390/ph14090924. PMID: 34577624; PMCID: PMC8465143. The primary outcomes for acute attacks should be freedom from migraine pain at two hours and freedom from the most bothersome symptom at two hours. Time from infusion until resolution of pain, which is reported as primary endpoint should become the main secondary endpoint, together with the other several secondary measures and patient-reported outcome measures included. In the sections about Ethics and dissemination, reference to consent for dissemination needs to be quoted. The repository providing the trial registration number should be reported to allow consultation. The age inclusion criteria should be extended over the 65 years established by the Authors, since this fragile population is often excluded from migraine treatments clinical trials. Although stating the limitation of literature paucity driving sample size calculation, the literature leading to n=40 patients in 1:1 ratio is not reported and needs to be included. Also, the inclusion of a patients diary is suggested. Blinding of data analyses is suggested. Minor comments In the Abstract the relation to lignocaine should be clarified and the acronym SMITE should be explained (and not only in the title). Some abbreviations, e.g. ICHD-3, ADR, PI, MIDAS, HIT-6, and WPAI, are missing

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1, Dr. Paolo Martelletti, Sapienza University of Rome
We thank reviewer one for their kind comments and suggestions for the trial.
- “It is good to suggest to the Authors an interesting fact that the definition of Resistant and Refractory migraine has been codified by the European Headache Federation”
We were not aware of the codified definition of refractory migraine. In using the term ‘refractory status migrainosus’ we wished to describe that the current attack had not responded to standard treatments, not the state of the underlying disease in general as resistant or refractory. We have removed the word ‘refractory’ to avoid confusion.

- “Similarly, it should be reported the data related to the numerical importance of the accesses to the ER with a diagnosis of primary headache”.
We have added a comment in the introduction highlighting the frequency of presentation and importance of access to the ER.

Reviewer: 2, Dr. Zhong Wang, First Affiliated Hospital of Soochow University
We thank reviewer two for the helpful feedback and discussion on the study design.
- “Normally should be compared with high-quality evidence treatment, such as triptans and intravenous prochlorperazine or chlorpromazine, or understood as compared with all conventional clinical treatment.” … ”there is no high-quality clinical evidence for intravenous lidocaine therapy for migraine itself. Although recommended by guidelines, it is not an accepted clinical treatment for

migraine and is usually only attempted if triptans and prochlorazine have failed treatment, with limited clinical applicability."
We agree with reviewer two that triptans and intravenous prochlorperazine have high-quality evidence in the acute treatment of migraine, as highlighted in our manuscript. It is our personal view that given this established evidence, the role for a medication such as eptinezumab would be second line, where these medications have failed. We have constructed our trial accordingly, and specifically stated that only patients who have failed, or cannot receive these established treatments would be enrolled.
The rationale for choice of lignocaine as a comparator was three-fold 1) we feel an active comparator drug was the most ethical choice in patients who had a painful condition for three days, 2) lidocaine is commonly used locally in this clinical setting, and as highlighted in our manuscript recommended by 10% of AHS respondents, making it a clinically meaningful comparator, 3) there are no practical second-line options that have a high-quality of evidence, and so the use of lidocaine will provide clinically-meaningful data.

- "The title of the article should be amended to highlight the comparison between Eptinezumab and intravenous lignocaine"
We have updated the title with the full study title, which highlights the comparison between eptinezumab and intravenous lignocaine

- "Intravenous infusion eptinezumab 300mg compared with intravenous lidocaine injection for five consecutive days after admission, the first difference is administration is different, and the second difference is the time of receiving the drug. Whether there is an effect on the therapeutic effect, whether eptinezumab needs to be supplemented daily to maintain optimal drug concentration."
We agree that the two medications have different administration, and we will have placebo infusions to prevent un-blinding. Given the half-life of eptinezumab, we don't believe that daily supplementation will be required.

- "The article lacks a list of abbreviations."
We have added a list at the end of the manuscript

- "Is it contrary to our common understanding to put a cross on items in table 2."
Table two states the schedule of activities for the trial, and the cross marks on which study visits each activity occurs.

Reviewer: 3, Dr. Damiana Scuteri, University of Calabria
We thank reviewer three for the helpful feedback and highlighting several relevant manuscripts.
- "the novelty of this study is downgraded by PMID 34128999; and PMID: 34577624"
We thank the reviewer for drawing our attention to these bodies of work, and have included them in our manuscript.

- "The outcomes should be freedom from migraine pain at two hours and freedom from most bothersome symptom at two hours"
We have updated the manuscript to include these outcomes, and have submitted an amendment to the clinical trial registry.

- In the sections about Ethics and dissemination, reference to consent for dissemination needs to be quoted. The repository providing the trial registration number should be reported to allow consultation.
We have included that patients will be consented to the dissemination of information, and have provided the consent form as an attachment. The repository providing the trial registration number is provided (Australian and New Zealand Clinical Trials Registry (ANZCTR - ACTRN12621001616864).

- The age inclusion criteria should be extended over the 65 years established by the Authors, since this fragile population is often excluded from migraine treatments clinical trials.
We agree with the reviewer that the licensing trials have excluded elderly patients, which has limited the available data for treating clinicians. We chose our study population age restrictions to be in keeping with the licensing trials however, as this medication was not licensed in our jurisdiction when the trial was registered, so we wished to limit possible safety concerns and the power of this trial is not such to provide meaningful information on the safety and tolerability of this medication in an older cohort.

- Also, the inclusion of a patients diary is suggested.
Patients will keep a diary as part of the trial.

- Blinding of data analyses is suggested.
We have added a comment making it explicit that data analysis will be blinded.

- In the Abstract the relation to lignocaine should be clarified and the acronym SMITE should be explained (and not only in the title). Some abbreviations, e.g. ICHD-3, ADR, PI, MIDAS, HIT-6, and WPAI, are missing.
Abbreviations included and SMITE expanded in the abstract.

VERSION 2 – REVIEW

REVIEWER	Scuteri, Damiana University of Calabria
REVIEW RETURNED	30-Dec-2021

GENERAL COMMENTS	The Ms has improved a lot after the revision, but there are still some concerns regarding the lack of auditing, reported to be n/a in the SPIRIT checklist that has been included. Moreover, the literature originating sample size calculation has not been provided.

REVIEWER	Wang, Zhong First Affiliated Hospital of Soochow University, Department of Neurosurgery
REVIEW RETURNED	04-Jan-2022

GENERAL COMMENTS	This article describes in detail a randomized controlled trial of eptinezumab and intravenous lignocaine for status migraine inpatient treatment, with clear logic and clear protocol. It also describes in detail the background, research method, experimental design, statistical analysis and discussion of comparing the treatment effects of the two drugs. Compared with the previous article, which was more modified, the security and validity data collection scheme is comprehensive and systematic, but the article still has some problems： 1. The article is fundamentally flawed. Although some guidelines recommend intravenous lidocaine for migraine, this treatment is rarely used in clinical practice and carries significant cardiovascular risks. Comparing the efficacy and safety of

	eptinezumab and intravenous lignocaine in the treatment of status migraine is of low clinical significance. 2. After patients receive intravenous infusion of 300 mg of eptinezumab, whether a supplemental dose needs to be infused daily to achieve an effective concentration of the drug. In the control group, lignocaine was pushed intravenously for 5 days in a row. Whether the different ways of drug administration in the experimental and control groups would have some effect on the treatment results. 3. Five days of hospitalization and the third follow-up was 140 days. The discomfort that occurred for a longer period of time after treatment could not be attributed to adverse effects due to drug therapy. 4. Table 2 is represented by a fork in the to-do list, which is not in compliance with conventional cognition.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2 – Dr. Zhong Wang

- The article is fundamentally flawed. Although some guidelines recommend intravenous lidocaine for migraine, this treatment is rarely used in clinical practice and carries significant cardiovascular risks. Comparing the efficacy and safety of eptinezumab and intravenous lignocaine in the treatment of status migraine is of low clinical significance.

While we respect that the reviewer may rarely use lidocaine in their clinical practice, as we have discussed in our article, it is not a rare inpatient treatment for status migrainosus internationally, as evidenced by the recent survey of the American Headache Society. Furthermore, it is a frequently utilised treatment in Australian Hospitals, where this trial is based. Secondly, as discussed in previous revisions, we believe that the utilisation of an active comparator is both ethically justified, and provides a high quality of evidence, beyond that had we simply run a placebo-controlled trial with no active comparator, which will remain of relevance for clinicians who do not use lidocaine.

- After patients receive intravenous infusion of 300 mg of eptinezumab, whether a supplemental dose needs to be infused daily to achieve an effective concentration of the drug. In the control group, lignocaine was pushed intravenously for 5 days in a row. Whether the different ways of drug administration in the experimental and control groups would have some effect on the treatment results.

Dosing studies of eptinezumab have been performed previously in the development of this medication (10.1186/s10194-021-01220-y). Whether the two medications exert a different effect in the timing of abortion of status migrainosus is indeed one of the outcome measures that is being assessed – this is of clinical significance, both in the duration of pain for patients, and the utilisation of healthcare resources.

- Five days of hospitalization and the third follow-up was 140 days. The discomfort that occurred for a longer period of time after treatment could not be attributed to adverse effects due to drug therapy.

The duration of follow-up was suggested by the sponsor as a longest possible follow-up in order to capture any possible adverse or unexpected event within five half-lives of the drug, such as pregnancy. This is a safety outcome, however we agree that a new 'discomfort' at this point would be not attributable to the study medication.

- Table 2 is represented by a fork in the to-do list, which is not in compliance with conventional cognition.

I regret that I do not understand this comment. Table 2 outlines the study activities that will be performed, which in addition with the protocols for administration would properly allow the replication of our trial, hence its inclusion.

Reviewer #3 – Dr. Damiana Scuteri

- The lack of auditing

The trial will be subjected to audit by the local HREC, and internal checking of data entry will be utilised to ensure accuracy. Interim analysis of results will not be performed due to the small sample size. We have included this in the article.

- The literature originating sample size calculation

At the time of development of the study, there was no published data regarding the efficacy of eptinezumab in acute migraine to determine a sample size. As such, and as described in the article, a study of forty patients was chosen, and the significance level and hazard ratio calculated, based on this and standard assumptions of an 80% power.

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