

# BMJ Open Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance (Mobile Stroke Unit—TASTE-A): protocol for a prospective randomised, open-label, blinded endpoint, phase II superiority trial of tenecteplase versus alteplase for ischaemic stroke patients presenting within 4.5 hours of symptom onset to the mobile stroke unit

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## ABSTRACT

**Introduction** Mobile stroke units (MSUs) equipped with a CT scanner are increasingly being used to assess and treat stroke patients' prehospital with thrombolysis and transfer them to the most appropriate hospital for ongoing stroke care and thrombectomy when indicated. The effect of MSUs in both reducing the time to reperfusion treatment and improving patient outcomes is now established. There is now an opportunity to improve the efficacy of treatment provided by the MSU. Tenecteplase is a potent plasminogen activator, which may have benefits over the standard of care stroke lytic alteplase. Specifically, in the MSU environment tenecteplase presents practical benefits since it is given as a single bolus and does not require an infusion over an hour like alteplase.

**Objective** In this trial, we seek to investigate if tenecteplase, given to patients with acute ischaemic stroke as diagnosed on the MSU, improves the rate of early reperfusion.

**Methods and analysis** TASTE-A is a prospective, randomised, open-label, blinded endpoint (PROBE) phase II trial of patients who had an ischaemic stroke assessed in an MSU within 4.5 hours of symptom onset. The primary endpoint is early reperfusion measured by the post-lysis volume of the CT perfusion lesion performed immediately after hospital arrival.

**Ethics and dissemination** The study was approved by the Royal Melbourne Hospital Human Ethics committee.

## Strengths and limitations of this study

- The testing of a potentially more effective thrombolytic agent for acute ischaemic stroke in the prehospital setting.
- There are practical, pharmacological and cost benefits of tenecteplase, which are ideally suited to the prehospital environment.
- An adequate but modest sample size given the clinical setting.
- The first prehospital study of tenecteplase for ischaemic stroke

The findings will be published in peer-reviewed journals, presented at academic conferences and disseminated among consumer and healthcare professional audiences.  
**Trial registration number** NCT04071613.

## INTRODUCTION

Ischaemic stroke is a major public health problem, for which effective and accessible drug therapies remain limited. Current management of acute ischaemic stroke includes treatment with recombinant tissue plasminogen activator (tPA, or alteplase) to lyse clots in cerebral arteries. Alteplase was

first proven for the treatment of patients with acute ischaemic stroke in the National Institutes of Neurological Disorders and Stroke (NINDS) trial in 1995, in a cohort of 600 patients.<sup>1</sup> The NINDS trial demonstrated doubling of the odds of an excellent clinical outcome at 90 days in patients treated with alteplase, despite an increase in the rate of major (symptomatic) intracerebral haemorrhage of 6%.<sup>2,3</sup> The treatment effect was much greater if given within 90 min of stroke onset. Subsequent trials and meta-analyses have confirmed that the treatment effect of alteplase is enhanced by earlier administration after stroke onset.<sup>4</sup> This emphasises that the management of acute ischaemic stroke is a medical emergency, and administering thrombolysis is a time-critical therapy. The need to deliver effective therapies in a timely manner has been a focus of clinical practice in stroke for decades and is often used as a performance benchmark for hospitals around the world. The evidence supporting the need for rapid treatment is substantial, and it has been demonstrated that each minute reduction in onset-to-treatment time resulted in a saving of 4.4 disability-adjusted life days after stroke (95% CI, 1.3 to 7.5 days,  $p=0.006$ ).<sup>5</sup> However, if there is recanalisation, each 1 min decrease in onset-to-treatment time saves an even greater amount of disability-adjusted life days (10.9 days,  $p<0.001$ ).

### Mobile stroke unit treatment dramatically improves stroke onset to thrombolysis treatment times

The mobile stroke unit (MSU) was first designed as a CT-equipped ambulance that enabled assessment and treatment of patients who had a stroke in the prehospital setting.<sup>6</sup> There are various staffing models but the Melbourne MSU, Australia's first, is staffed by a stroke neurologist, stroke nurse, a CT radiographer and two paramedics. The MSU is dispatched and will attend a suspected stroke patient at the site where their stroke occurs (typically their residence). The MSU provides a unique platform to administer thrombolysis and other stroke treatment (such as blood pressure lowering for intracranial haemorrhage (ICH)) within the hyperacute period. As a result, the MSU has been developed with the aim of delivering thrombolysis to stroke patients' prehospital, with a number of MSUs active around the world.<sup>7</sup>

The use of an MSU in Homburg, Germany, resulted in halving of the median onset to treatment for ischaemic stroke from 153 to 72 min, while in Berlin, Germany, the MSU increased the rate of thrombolysis within the first 60 min sixfold (from 4.9% to 31%).<sup>8</sup> The Melbourne MSU has treated 10 times more patients in the first 60 min compared with hospital-based thrombolysis and shown major time savings for thrombolysis and thrombectomy.<sup>9</sup> We have also shown that stroke treatment in the MSU is cost-effective.<sup>10</sup> Treatment of intracerebral haemorrhage is also facilitated by the MSU.<sup>11</sup> Recent phase III trials in Europe and the USA have shown that prehospital stroke management with thrombolysis improves 90-day clinical outcomes.<sup>12,13</sup>

### Tenecteplase is potentially a more effective and safer thrombolytic

With the enhanced access to timely treatments for potential stroke patients via the MSU,<sup>14</sup> there is also the potential to test more effective thrombolytic agents.<sup>15</sup> Alteplase leads to recanalisation of the occluded vessel in only 30%–50% of ischaemic stroke cases, and this rate may be lower with larger more proximal clots causing large vessel occlusion (LVO). Tenecteplase is currently being tested in several large in-hospital trials around the world to identify if it is a more effective stroke thrombolytic therapy than alteplase. Tenecteplase is a genetically engineered mutant tPA that has a longer half-life (allowing single bolus administration rather than an infusion), is more fibrin-specific and is more resistant to plasminogen activator inhibitor-1 than alteplase. These pharmacological differences appear to result in more rapid thrombolysis for tenecteplase and less bleeding complications than bioequivalent doses of alteplase and have led to tenecteplase becoming the first-line thrombolytic for ST-segment elevation myocardial infarction (STEMI) if percutaneous coronary intervention cannot be performed within 120 min from the time of STEMI diagnosis.<sup>16,17</sup> It is now used in the prehospital setting for MI and its benefit is now such that ambulance staff are providing it in the field after a cardiologist reviewed ECG.<sup>18</sup> Additionally, tenecteplase has substantial practical benefits, in that it is much easier to administer, being a single bolus administration (rather than a bolus followed by a 1-hour infusion for alteplase). In stroke, tenecteplase may similarly offer enhanced reperfusion over the current standard of care alteplase when administered in a timely manner.

There have now been four completed randomised clinical trials comparing the effectiveness of tenecteplase to alteplase in patients who had an ischaemic stroke. An Australian phase II tenecteplase study found significantly higher rates of reperfusion and vessel recanalisation compared with alteplase, which in turn translated into much better clinical outcomes. This study assessed two doses of tenecteplase, the higher dose assessed (0.25 mg/kg) being clearly superior.<sup>19</sup> This trial used 'dual target' imaging selection criteria; vessel occlusion on CT angiography (CTA) and presence of salvageable tissue on CT perfusion (CTP) (small core and large penumbra). Next, a Scottish phase II study<sup>20</sup> was also performed but failed to show a 3-month clinical benefit from treatment with tenecteplase (0.25 mg/kg), although CTA and CTP imaging selection was not used. However, subsequent pooling of data for the Scottish and Australian studies showed substantial clinical benefit and less serious brain haemorrhage in patients treated with tenecteplase in the patients with a dual imaging target.<sup>21</sup> Another recently completed Australian phase II trial (EXTEND IA TNK) used the same dual target imaging selection approach as the first tenecteplase study in patients pre-thrombectomy, and again, found that tenecteplase (0.25 mg/kg) led to superior recanalisation (pre-thrombectomy) compared with alteplase and better clinical outcomes.<sup>22</sup> A large

(1100 patient) Norwegian phase III RCT of a higher dose of tenecteplase (0.4mg/kg) versus 0.9mg/kg alteplase (NOR-TEST) did not use imaging selection nor measure reperfusion as an outcome. This study was limited by a mild stroke patient population (median NIHSS 4), and 17% of patients included had stroke mimics. NOR-TEST found no difference in 3-month outcomes but reassuringly, despite the higher dose of tenecteplase, but did not show a higher rate of brain haemorrhage with the 0.4mg/kg dose to establish the safety profile of tenecteplase.<sup>23</sup> Finally, our Australian group showed no advantage in reperfusion of the 0.4mg/kg dose compared with 0.25mg/kg in patients with LVO, planned for thrombectomy.<sup>24</sup>

With these extremely encouraging trial results, the next logical step is to test tenecteplase in an MSU setting, given that it seems more effective at quickly dissolving clots in brain arteries and may result in similar or reduced brain haemorrhage rates. Additionally, the single bolus administration of tenecteplase is much more practical in the pre-hospital MSU setting, and tenecteplase may be less expensive per patient treated. Therefore, there is a clear rationale for examining the earlier use of a more effective thrombolytic agent (tenecteplase) for patients who had an ischaemic stroke treated in the MSU.

In the present study, we aim to test the hypothesis that treatment of patients identified as suspected ischaemic stroke with tenecteplase on the MSU will result in greater earlier reperfusion compared with the current standard of care, alteplase. The secondary aims are to determine whether treatment with tenecteplase in the MSU results in improved patient clinical, radiological and safety outcomes compared with alteplase. We will also examine if there are improvements in treatment times on the MSU with tenecteplase.

## METHODS AND ANALYSIS

### Design

The study will be a prospective, randomised, open-label, blinded endpoint (PROBE) phase II superiority trial (2 arms with 1:1 randomisation) with adaptive sample size

re-estimation in patients identified as suspected ischaemic stroke in the MSU. It is planned that there will be one centre (the Melbourne MSU with follow-up performed at the receiving hospitals). Patients will be randomised to treatment with either standard of care alteplase (0.9mg/kg) or the investigational product tenecteplase (0.25mg/kg). Randomisation will be stratified according to baseline NIHSS (<6 and ≥6) to secure equal allocation in the two groups.<sup>25</sup> The study procedure and assessment are illustrated in figure 1.

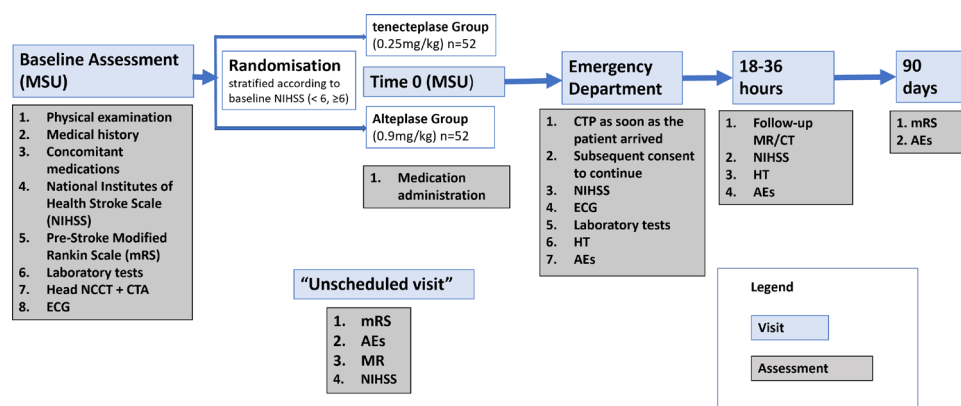
### Patient population—inclusion and exclusion criteria

#### Inclusion criteria

1. Patients with a suspected acute ischaemic stroke in the MSU who are eligible for thrombolysis using standard clinical criteria.
2. Patient's age is ≥18 years.
3. Premorbid modified Rankin Scale (mRS) 0–3.

#### Exclusion criteria

1. ICH or other diagnosis (eg, tumour) identified by CT on the MSU.
2. Hypodensity in >1/3 middle cerebral artery territory or equivalent proportion of anterior cerebral artery or posterior cerebral artery territory on non-contrast CT on MSU.
3. Rapidly improving symptoms at the discretion of the investigator.
4. Pre-stroke mRS score of >3 (indicating previous moderate to severe disability).
5. Participation in any investigational study in the previous 30 days.
6. Any terminal illness such that patient would not be expected to survive more than 1 year.
7. Any condition that, in the judgement of the investigator, could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.
8. Pregnant women.
9. Previous stroke within last 3 months.
10. Recent past history or clinical presentation of ICH, subarachnoid haemorrhage, arterio-venous



**Figure 1** Study assessments and procedures. AEs, adverse events; CTA, CT angiography; HT, haemorrhagic transformation; MSU, mobile stroke unit.



- malformation, aneurysm or cerebral neoplasm. At the discretion of each Investigator.
11. Current use of vitamin K-based oral anticoagulants (eg, warfarin) and a prolonged prothrombin time (INR >1.5) measured on point of care testing.
  12. Current use of novel oral anticoagulants (ie, rivaroxaban or apixaban). Patients taking dabigatran can be treated if they are given the reversal agent (idarucizumab) prior to thrombolysis.
  13. Use of heparin, except for low-dose subcutaneous heparin, in the previous 48 hours and a prolonged activated partial thromboplastin time exceeding the upper limit of the local laboratory normal range.
  14. Use of glycoprotein IIb–IIIa inhibitors within the past 72 hours. Use of single or dual agent oral platelet inhibitors (clopidogrel and/or aspirin) prior to study entry is permitted.
  15. Clinically significant hypoglycaemia.
  16. Uncontrolled hypertension defined by a blood pressure >185 mm Hg systolic or >110 mm Hg diastolic on at least two separate occasions at least 10 min apart or requiring aggressive treatment to reduce the blood pressure within these limits. The definition of ‘aggressive treatment’ is left to the discretion of the responsible investigator.
  17. Hereditary or acquired haemorrhagic diathesis.
  18. Gastrointestinal or urinary bleeding within the preceding 21 days.
  19. Major surgery within the preceding 14 days which poses risk in the opinion of the investigator.
  20. Exposure to a thrombolytic agent within the previous 72 hours.
  21. A known hypersensitivity to the active substance alteplase, tenecteplase, gentamicin or to any of the excipients.

### Consent and randomisation

Under local Victorian law, the human research ethics committee have approved emergency treatment provisions (without informed consent) with subsequent consent to continue follow-up in the study. This is based on the time-critical nature of thrombolytic treatment, which would make delaying standard care unethical and the expected risk/benefit profile of the intervention versus standard care given tenecteplase extensive safety profile from stroke and other trials.

### Patient consent

At the time of treatment, the patients or medical treatment decision-maker (if the patient is not able to consent) will have the study explained as per the Participant Information Sheet (short version) and, if they agree, will be asked to complete a Participant Short Consent Form. As soon as following treatment and arrival in the hospital, the patient will be given the Participant Information and Consent Form (Continuation after short consent). Each participant (or medical treatment decision-maker where this is applicable) will be given a full explanation of the nature and purposes of the study and a copy of

the information sheet to review. Once the essential study information has been provided, and the investigator is assured that each patient or their representative understands the implications of participating or continuing in the study as appropriate, the patient or their medical treatment decision-maker will be asked to give consent to the study by signing the informed consent form.

Patients will be randomised to receive either the investigational drug (tenecteplase) or standard care (alteplase) according to a randomisation schedule with blocks of randomly varying sizes, with stratification for baseline NIHSS at a cut point of 6 (<6 and ≥6). The MSU will be equipped with two boxes (one for each severity stratum) containing individual closed envelopes with individual treatment allocations, organised within boxes in sequential order of randomisation, to be used for individual patients. This arrangement provides a convenient way for investigators to access the randomised study medication within the stroke MSU with minimal effort.

### Treatment or intervention

The investigational product tenecteplase (Metalyse, Boehringer Ingelheim) is a genetically modified form of tPA. Within this study, tenecteplase lyophilised powder will be reconstituted in a glass vial with water for injection at concentration 5 mg/mL (eg, 40 mg tenecteplase in 8 mL water). Vials should be maintained at a temperature less than 30°C and protected from light as per the manufacturer's product information.

After reconstitution of the investigational product, a dedicated IV cannula should be used for administration. The dose of tenecteplase to be administered is 0.25 mg/kg (maximum 25 mg), given as a bolus over approximately 5s. The investigational product should be used immediately after reconstitution. No other anticoagulants or antiplatelet agents are to be given within 24 hours of administration of the investigational product.

Patients enrolled in the trial can proceed to thrombectomy if the local treating team deem the patient eligible, and this is not an exclusion from the trial provided that the patient undergoes a CTP scan prior to thrombectomy following trial treatment.

### Data management

Data will be recorded in an electronic case report form. Access to the database will be secure and password protected and managed by Data Managers at The Melbourne Brain Centre at the Royal Melbourne Hospital. Access to the system will only be granted after documented training. All information collected for this study will have identifying information removed and be kept private, confidential and secure. Data will be stored in a re-identifiable/coded format for safety purposes.

### Blinding/unblinding

The investigational treatment is open-label. All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation.

The Data Safety Monitoring Board (DSMB) will have access to unblinded grouped data.

### Primary outcome

The volume of the perfusion lesion on CTP imaging performed on arrival at the receiving hospital, adjusted for pre-treatment NIHSS and time from initiation of treatment to CTP, compared between the two treatment groups. Perfusion imaging will be processed by an automated programme AutoMISTar (supplied by Apollo, Melbourne, Australia). Perfusion lesion will be defined by a delay time (DT) of  $>3$  s<sup>26 27</sup> for both CTP and MR perfusion imaging

### Secondary outcomes

#### Efficacy (imaging)

- ▶ Per cent reperfusion between baseline CTP and 24-hour perfusion imaging (MRI/CTP).
- ▶ Ischaemic core growth between baseline CTP and 24-hour MRI/CT.

#### Efficacy (clinical)

- ▶ Reduction in NIHSS between pre-treatment score and score on ED arrival, adjusted for pre-treatment NIHSS and time from initiation of treatment to ED NIHSS score.
- ▶ Reduction in NIHSS between pre-treatment score and score at 24-hour post treatment, adjusted for pre-treatment NIHSS.
- ▶ mRS at 3 months—ordinal analysis adjusted for baseline NIHSS and age
- ▶ mRS 0–1 or no change from baseline at 3 months adjusted for baseline NIHSS and age.
- ▶ mRS 0–2 or no change from baseline at 3 months adjusted for baseline NIHSS and age

#### Process measures

- ▶ Proportion of patients where thrombolytic medication is initiated within 5 min of completion of CT on the MSU.
- ▶ Time from completion of CT on the MSU to initiation of thrombolysis (CT to needle time)

#### Safety outcomes

- ▶ mRS 5–6 at 3 months adjusted for baseline NIHSS and age.
- ▶ Death due to any cause adjusted for baseline NIHSS and age.
- ▶ Any parenchymal haematoma.
- ▶ Symptomatic intracranial haemorrhage (sICH), defined as 'Intracerebral haemorrhage (parenchymal haematoma type 2 within 36 hours of treatment) combined with neurological deterioration leading to an increase of  $\geq 4$  points on the NIHSS from baseline or the lowest NIHSS value between baseline and 24 hours'.<sup>28</sup>

### Data monitoring body

Study monitoring and quality of assurance will be undertaken internally by a study coordinator who does not have

primary patient contact, based at the Royal Melbourne Hospital in the Melbourne Brain Centre in accordance with Good Clinical Practice guidelines.

In order to ensure the accuracy of data, direct access to source documents by the study coordinator will be required. Anonymity of the subject will be maintained at all times.

The trial will be managed by a steering committee. An independent DSMB will also be implemented to review the safety and feasibility of the trial. To compare the safety of IV tPA therapy versus IV TNK, two safety parameters—mortality at 3 months and the incidence of sICH within 36 hours of intervention, will be monitored by the independent DSMB after 50 patients have been enrolled. If there are concerns about the safety of participants, DSMC will make a recommendation to the trial steering committee about continuing, stopping or modifying the trial. The Haybittle-Peto boundary procedure for generating early stopping boundaries will be used. A recommendation of early termination due to safety reasons will be considered by the DSMC if the corresponding Haybittle-Peto boundary ( $p=0.001$ ,  $Z=3$ ) at a given interim analysis is crossed.

### Sample size estimates

Based on the data from the phase II and III Australian tenecteplase trials and experiences with the MSU, an estimated total sample size of 104 patients (with 52 patients in each treatment and control arms) yields 90% power to detect a hypothesised mean difference of 13 mL (SD 20 mL) in the perfusion lesion volume between treatment groups measured at the receiving hospital at a statistical significance threshold of  $p=0.05$ . The ongoing TASTE trial has a mean pre-treatment perfusion lesion volume of 65 mL (SD 20 mL). In phase II Australian tenecteplase trial, the post-treatment (24 hours) perfusion lesion was 50% smaller in the tenecteplase arm. Given post-treatment CTP will be performed considerably earlier in TASTE-A, we have assumed a more conservative 20% difference in post-treatment perfusion lesion.<sup>10</sup>

Adaptive increase in sample size is planned based on the result of interim analysis using data from the first 80 patients, as per Mehta and Pocock.<sup>29</sup> The maximum sample size is capped at 200 patients, with a minimum of 104.

A blinded review of the perfusion lesion volume was conducted based on the first 80 participants. It revealed that the more appropriate model was a zero-inflated negative binomial (ZINB) regression model with the perfusion volume expressed as a count of millilitres of perfusion lesion. The ZINB model accounts for the potential overdispersion in the perfusion lesion volume distribution and the potential presence of stroke mimics among the RCT participants.

We performed the sample size re-estimation using the ZINB regression and found no need for an adaptive increase in the sample size. Therefore, the final sample size was 104.

## Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## Statistical analyses

The analysis will be based on intention-to-treat principles. The primary outcome—the difference in volume of the perfusion lesion between patients treated with tenecteplase and alteplase at the receiving hospital was originally planned to be investigated using a linear regression model (subject to the satisfiability of the relevant assumptions, otherwise median regression) with the treatment group as an input, and baseline NIHSS and time from treatment to CTP in ED as covariates. Following a blinded review of the distributional properties of the volume of the perfusion lesion based on the first 80 patients, the more appropriate model was deemed to be a ZINB regression model with perfusion volume expressed as a count of the perfusion lesion volume in millilitres. ZINB model accounts for the potential overdispersion in the perfusion lesion volume distribution as well as for the potential presence of stroke mimics (ie, patients without stroke who may be originally diagnosed as having stroke on MSU, but will have zero volume of the perfusion lesion) in the study sample. Thus, the primary outcome will be investigated using a ZINB regression model with the volume of the perfusion lesion expressed as the count of millilitres, the treatment group as an input, and baseline NIHSS and time from treatment to CTP in ED as covariates. The effect size will be presented as the ratio of expected volumes in patients with tenecteplase and patients with alteplase with respective 95% CI.

The extent of 24-hour reperfusion and infarct core growth will be compared using appropriate regression models. The extent of early clinical improvement (pre-treatment to ED NIHSS) and 24-hour clinical improvement will be compared respectively using the appropriate regression models, with pre-treatment NIHSS as a covariate. Functional outcomes—mRS scores at 3 months—will be compared using an appropriate regression model with both baseline NIHSS and age as covariates. Ordinal analysis of mRS will be performed using an ordinal regression model subject to the proportional odds assumption being satisfied or otherwise using an assumption-free method based on generalised ORs. The final hospital diagnosis and the presence of stroke mimics will also be reported.

A detailed statistical analysis plan (SAP) document will be developed and finalised prior to the study database lock.

## Missing data handling

At the time of finalisation of the study SAP, clinical input from the TASTE-A management committee will be sought as to whether the primary outcome can be assumed to be missing at random. Important explanatory and auxiliary variables are collected and will be examined to assess the

plausibility of the missing at random assumption. Sensitivity analyses that consider a range of plausible alternative assumptions about the missing primary outcome data will be conducted as per the strategy described in White *et al.*<sup>30</sup>

## Ethics and dissemination

This study is centrally coordinated from the Melbourne Brain Centre, with central human ethics and research approval from the Royal Melbourne Hospital (ethics reference number: HREC/18/MH/6), and governance approval from the respective destination hospitals (The Alfred Hospital, Monash Hospital, Western Hospital, The Austin Hospital and Box Hill Hospital). The study has engaged with a blinded external data monitor to ensure that all information collected is a true and accurate representation as well as to ensure data completeness. Patient follow-ups are collected centrally either in person or over the phone by a blinded assessor. On study recruitment completion and participant follow-up, the study will be formally closed and published in a peer-reviewed journal.

## DISCUSSION

TASTE-A is the first, prospective randomised, open-label, blinded endpoint, phase II superiority trial of tenecteplase versus alteplase for patients who had an ischaemic stroke presenting within 4.5 hours of symptom onset to the mobile stroke unit. This study is a significant step toward reducing the burden of ischaemic stroke by combining multiple advances, that is, the implementation of earlier treatment with the MSU model of care, novel imaging biomarkers used by the study to assess both patient status and outcome, and the testing of a potentially more effective and more practical thrombolytic agent. The practical and pharmacological benefits of tenecteplase are ideally suited to the mobile stroke unit environment. However, it is important to acknowledge that the MSU model of care is currently operating in limited regions around the world, despite their proven efficacy. Furthermore, we only use imaging marker as the primary outcome in this study; considering that this trial is a phase II trial and ultimately restricted to one MSU, the chosen endpoint also results in a feasible sample size. Should this trial be successful, then a follow-up phase III could be powered using data from this phase II trial a. If the study outcome is positive, it would provide significant evidence for a randomised, multicentre, phase III trial assessing the efficacy of tenecteplase versus alteplase for patients who had an ischaemic stroke in the mobile stroke unit and acute setting.

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**Contributors** AB, LC, HZ, BC, BY, SD, GD and MP planned the study and developed the protocol. AB, LC, SC, NY, MV, AS, AB, ADS, FN, FL, MP, MS, KS, SB, VT, GC, PC, HM, TW, LO and CC participated in the protocol writing and project administration. All authors contributed to editing and approved the final draft of the manuscript and data acquisition.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The trial was approved by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/6)

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