

# Rationale and design of Treatment of Acute Ischaemic Stroke with Edaravone Dexborneol II (TASTE-2): a multicentre randomised controlled trial

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## ABSTRACT

**Background** Edaravone dexborneol is believed to be a novel cytoprotective drug, demonstrating a synergistic combination of antioxidative and anti-inflammatory properties in animal models. The Treatment of Acute Ischaemic Stroke with Edaravone Dexborneol (TASTE) trial demonstrated its superior efficacy over edaravone alone for acute ischaemic stroke (AIS) patients. However, its efficacy in individuals undergoing endovascular therapy (EVT) remains uncertain.

**Aim** To clarify the rationale and design of the TASTE II (TASTE-2) trial.

**Design** The TASTE-2 is a multicentre, double-blind, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of edaravone dexborneol in patients with AIS and large-vessel occlusion in the anterior circulation. The eligible participants, presenting with a National Institute of Health Stroke Scale score between 6 and 25 (range 0–42, with larger values suggesting severe neurological dysfunction) and an Alberta Stroke Program Early Computed Tomography Score ranging from 6 to 10 (range 0–10, with smaller values suggesting larger infarction) within the initial 24 hours after symptom onset, will be randomly allocated to either the edaravone dexborneol group or the placebo group in equal proportions prior to thrombectomy. The treatment will be continuously administered for a duration of 10–14 days. A follow-up period of 90 days will be implemented for all participants.

**Study outcomes** The primary efficacy outcome is defined as achieving favourable functional independence, measured by a modified Rankin Scale of 0–2 at 90 days. The primary safety outcome focuses on the incidence of serious adverse events.

**Discussion** The TASTE-2 trial will provide evidence to determine whether the administration of edaravone dexborneol in AIS patients undergoing EVT could yield significant improvements in neurological function.

## INTRODUCTION AND RATIONALE

Reperfusion therapy, namely intravenous thrombolysis (IVT) and endovascular therapy (EVT), has been highly recommended to individuals diagnosed with major ischaemic stroke (IS), particularly those with large-vessel occlusion (LVO), however, the proportion of unfavourable functional outcome

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Edaravone dexborneol has been proved to be cytoprotective in improving functional outcome of acute ischaemic stroke (AIS) patients when compared with edaravone alone, however, whether it is efficacious and safe in AIS patients who will undergo endovascular therapy (EVT) remains unclear.

### WHAT THIS STUDY ADDS

⇒ The treatment of acute ischaemic stroke with edaravone dexborneol II is the first phase III trial of edaravone dexborneol prior thrombectomy in AIS patients.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Data obtained from this trial will offer valuable evidence of edaravone dexborneol in AIS patients with EVT.

remains as high as 54% in the five classical trials of EVT.<sup>1</sup> Brain cytoprotection, formerly known as neuroprotection, had been highly expected to improve functional outcome of IS but failed to show their benefits so far in randomised clinical trials.<sup>2,3</sup> Considering the rapid advancement of thrombectomy techniques and devices aimed at improving functional outcome in patients with LVOs effectively in the era of reperfusion and to have maximum impact of cytoprotectants, the Stroke Treatment Academic Industry Roundtable (STAIR) recommended to clinically evaluate cytoprotective agents alongside reperfusion therapy, for which multiple mechanisms of brain ischaemia or reperfusion injury had been elucidated.<sup>4–6</sup> Therefore, a strategy using multitarget cytoprotectant agents which act through various synergistic mechanisms to prevent ischaemic injury was recommended with priority.<sup>4–6</sup>

Edaravone, approved to treat amyotrophic lateral sclerosis by the US Food and Drug Administration, has proven to be cytoprotective through early scavenging of free



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radicals and later exerting anti-inflammatory effects to promote functional recovery and structural integrity in reperfusion animal models.<sup>7–9</sup> Furthermore, a retrospective observational study has shown that edaravone was associated with greater functional independence in stroke patients who underwent EVT.<sup>10</sup> While (+)-borneol was estimated to have potent cytoprotective effects through multiple mechanisms in IS models, like inhibiting neuronal excitotoxicity through potentiating  $\alpha 2/\alpha 3$ -containing GABAA receptors, regulating the expression of nitric oxide synthase, suppressing  $\text{Ca}^{2+}$  overload and reducing the release of reactive oxygen species.<sup>11–14</sup> Being combined together with a ratio of 4:1, edaravone dexborneol has been demonstrated to be a brain cytoprotective agent that exhibits synergistically antioxidative and anti-inflammatory effects and downregulating ferroptosis to attenuate reperfusion injury in preclinical models<sup>15–18</sup> and has been proved to be efficacious in improving functional recovery among IS patients within 48 hours when compared with edaravone alone in Treatment of Acute Ischaemic Stroke (AIS) with Edaravone Dexborneol (TASTE) trial.<sup>19</sup> However, whether it is cytoprotective as a whole in those patients who are treated with EVT has not been confirmed.

Therefore, we launched the TASTE II (TASTE-2) trial to test the efficacy and safety of edaravone dexborneol in improving functional outcome for those patients undergoing EVT because of LVO.

## METHODS

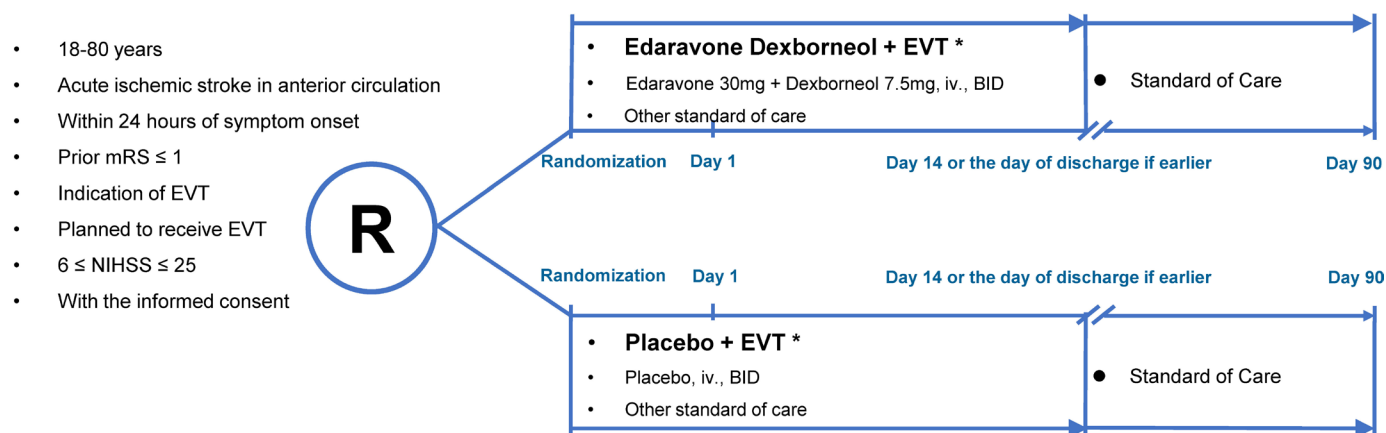
### Study design and patient population

The TASTE-2 is a multicentre, double-blind, randomised, placebo-controlled trial aiming to evaluate the efficacy and safety of edaravone dexborneol in AIS individuals who will receive EVT. All enrolled patients will be randomised with 1:1 to edaravone dexborneol or placebo within 24 hours of symptom onset and receive continuous

application for 10–14 days. All these participants will receive standard medical care afterwards and be followed up for 3 months (figure 1).

This trial will include patients who are diagnosed with AIS, aged between 18 and 80 years, with a National Institutes of Health Stroke Scale (NIHSS) score between 6 and 25 (range 0–42, with larger values suggesting severe neurological dysfunction) and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6–10 (range 0–10, with smaller values suggesting larger infarction). All these patients should be characterised with an anterior LVO at intracranial internal carotid artery, T-shaped bifurcation or the M1 segment of middle cerebral artery and are to undergo treatment with EVT within 24 hours after symptom onset, however, prior or concomitant IVT with alteplase is not prohibited if indicated. Additionally, an imaging evaluation of mismatch should be performed through an automated software and the criteria of DEFUSE-3<sup>20</sup> or DAWN<sup>21</sup> should be met for those within 6–24 hours after symptom onset. This software will be used to calculate the infarct core volume, mismatch ratio and mismatch volume (figure 2), of which rationale and details (Patents no. ZL202110266924.6 and ZL202110226735.6) has been described elsewhere.<sup>22</sup>

Patients will be excluded if CT scan indicating intracranial haemorrhagic diseases, being given any IVTs other than alteplase before EVT, being allergic to any components of edaravone dexborneol injection, having a history of congenital or acquired haemorrhagic disease, with an elevated systolic blood pressure surpassing 180 mm Hg or diastolic blood pressure exceeding 110 mm Hg after therapy, being in cases where the serum levels of alanine aminotransferase or aspartate transaminase are found to exceed three times the upper limit of normal, or if the current serum creatinine exceeds 1.5 times the upper limit of normal, or if the estimated glomerular



\*EVT including bridging therapy, which patients receive intravenous alteplase before mechanical thrombectomy, and direct mechanical thrombectomy

**Figure 1** TASTE-2 study design. EVT, endovascular therapy; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TASTE-2, Treatment of Acute Ischaemic Stroke with Edaravone Dexborneol II.

### The inclusion criteria

1. 18 to 80 years, for both males and females
2. Clinically diagnosed with AIS presenting anterior circulation large vessel occlusion (LVO), specifically involving the terminal portion of the intracranial carotid artery, T-shaped bifurcation, or M1 segment of middle cerebral artery
3. Within 24 hours from the initiation of stroke
4. Qualified for additional imaging indications related to bridging therapy or direct mechanical thrombectomy:
  - The ASPECTS score should be  $\geq 6$  as certified by the latest brain CT scan
  - Patients within 6 to 16 hours after stroke onset should meet the mismatch criteria, which are defined as an infarction core volume  $< 70$  ml, a mismatch ratio  $\geq 1.8$ , and an ischaemic volume  $> 15$  ml (DEFUSE-3 criteria), [20] or an NIHSS score  $\geq 10$  with an infarct core volume  $< 31$  cm<sup>3</sup>, or an NIHSS score  $\geq 20$  with an infarct core volume  $\leq 51$  cm<sup>3</sup> (DAWN Criteria) [21]
  - Patients within 16 to 24 hours after stroke onset should also meet the mismatch criteria, which are defined as an NIHSS score  $\geq 10$  with an infarct core volume  $< 31$  cm<sup>3</sup>, or an NIHSS score  $\geq 20$  with an infarct core volume  $\leq 51$  cm<sup>3</sup> (DAWN Criteria) [21]
5. Planned to undergo bridging therapy (EVT after intravenous alteplase administration) or direct EVT
6. Pre-morbid modified Rankin Scale score  $\leq 1$
7. NIHSS score  $\geq 6$  but  $\leq 25$  prior to the EVT
8. Obtained signed informed consent from subjects or their authorized representatives

### The exclusion Criteria

1. CT scan confirmed intracranial hemorrhagic diseases, like hemorrhagic stroke, subarachnoid hemorrhage, ventricular hemorrhage, or subdural hematoma, etc.
2. Received any intravenous thrombolytic drug other than alteplase prior to bridging therapy
3. Be allergic to any components of edaravone dexborneol injection
4. Currently received edaravone, dexborneol, any Chinese traditional medicine containing borneol or any other cytoprotective agents
5. Having a history of coagulation factor deficiency disease, thrombocytopenic disease, or congenital or acquired hemorrhagic disease
6. With an elevated systolic blood pressure over 180 mmHg or diastolic blood pressure over 110 mmHg after antihypertensive therapy
7. The serum levels of ALT or AST are found to exceed 3 times the upper limit of normal
8. Recent or current serum creatinine exceeds 1.5 times the upper limit of normal, or the estimated glomerular filtration rate (eGFR) falls below 60 mL/min
9. Those who is in the state of pregnancy, lactation, or planned to be in the state of pregnancy within 90 days
10. Patients who cannot complete informed consent process and the follow-up treatment due to severe mental disorder or dementia
11. Those who is having malignant tumors, severe systemic diseases, or predicted survival time less than 90 days
12. Participated in another interventional study within 30 days before randomization

ALT, alanine aminotransferase; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; AST, aspartate transaminase; CT, computerized tomography; DAWN, DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE-3, Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke; EVT, endovascular therapy; NIHSS, National Institute of Health Stroke Scale.

**Figure 2** The inclusion and exclusion criteria of the TASTE-2 trial. TASTE-2, Treatment of Acute Ischaemic Stroke with Edaravone Dexborneol II.

filtration rate falls below 60 mL/min, etc (figure 2). Patients who have recently been administered or are currently receiving any Chinese traditional medicine containing borneol should also be excluded. Prior to enrolling patients, the trial must receive the endorsement from the Institutional Review Board at Beijing Tiantan Hospital, Capital Medical University and it is imperative to obtain written informed consent from every participant or their legally designated representative.

### Randomisation

The randomisation sequence will be produced by SAS V.9.4 software at the Statistical and Data Center of the National Clinical Research Center for Neurological Diseases in China prior to the trial's commencement, using a fixed-size block randomisation method. Each unique sequence number will be uniformly labelled on all the packages of the drug thereafter. This number will serve as the identifier of the drug in the smallest packaging unit and does not contain group information. All packaged drugs will be mailed to each site in randomisation sequence order with a minimum of one block. The eligible patients will be stratified based on the participating hospitals and randomly allocated to either the edaravone dextro-borneol group or the placebo group in equal proportions. After randomisation, the interventional drug should be given as soon as possible before the EVT is performed. Blinding will be maintained throughout the study.

### Intervention

Patients allocated to the intervention group will be given intravenous edaravone dextro-borneol 37.5 mg, comprising 30 mg of edaravone and 7.5 mg of (+)-dextro-borneol, two times a day over a consecutive period of 10–14 days lasting for 30 min each time. Meanwhile, patients allocated to the control group will be given intravenous placebo of edaravone dextro-borneol in the same manner. The placebo contains all ingredients except the active edaravone and (+)-dextro-borneol. The first dose injection of edaravone dextro-borneol or placebo must precede the treatment of EVT and no later than the puncture of femoral artery. IVT with alteplase will not be prohibited neither before nor after randomisation if indicated. For this trial, EVT will be performed as a fundamental treatment and the reperfusion status of occluded large vessels will be evaluated using the 7-point extended Thrombolysis in Cerebral Infarction (eTICI) scoring system, and a higher eTICI score suggests a more significant reperfusion. Successful reperfusion is determined by reaching an eTICI score of 2b50 or higher, indicating a minimum of 50%–66% restoration of blood flow.<sup>23</sup> Other standard of care can be used in both groups except those drugs that seem to be brain cytoprotective.

### Outcomes

The primary efficacy outcome is defined as achieving favourable functional independence, which is indicated by a modified Rankin Scale (mRS, a scale of 0–6, scores 0–2 representing independence and scores 3–6 indicating dependence or death) score of 0–2 at 90 days. This score will be assessed in person, or by a real-time video if a face-to-face visit is not feasible, by a certified rater who is blind to the group assignments. This rater will be trained periodically under a theoretical guidance.<sup>24</sup> The secondary efficacy outcomes encompass shift analysis of mRS, excellent functional outcome characterised by an mRS score of 0–1 at 90 days, the change in NIHSS score from 10 to 14 days to baseline, a decrease of NIHSS score  $\geq 4$  from 10 to 14 days to baseline, and the occurrence of new ischaemic or haemorrhagic stroke within 90 days. The primary safety outcome is the proportion of serious adverse events (SAEs) that occur throughout the entire study period. The secondary safety outcomes include all-cause mortality within 90 days, symptomatic intracranial haemorrhage within 36 hours, deterioration in neurological deficit defined as a  $\geq 4$ -point increase in the NIHSS score from day 1 to baseline, and the proportion of AEs within 90 days. All SAEs will be evaluated by an independent clinical events committee. The study will also involve the collection of blood samples for further investigation into potential mechanisms (table 1).

### Data Safety and Monitoring Board

To uphold ethical standards and prioritise patient safety, the data safety and monitoring board (DSMB) will convene according to the established protocol to carefully monitor the trial's progress. The DSMB, consisting of non-trial participants, will be entrusted with specific responsibilities outlined by the trial executive committee before its commencement. Following each meeting, DSMB will furnish written recommendations to the trial steering committee chairs.

### Sample size

According to the findings of the TASTE trial,<sup>19</sup> the edaravone dextro-borneol group showed a 13.9% relative increase in neurological improvement compared with the edaravone alone group. Taking into account the positive effect of edaravone as a control in the TASTE trial, it is assumed that there will be a 20% relative increase in neurological improvement when comparing edaravone dextro-borneol with placebo in the upcoming TASTE-2 trial. In ANGLE-ACT, a large cohort study including Chinese patients treated with EVT, 45.4% of patients achieved mRS scores of 0–2 within 90 days.<sup>25</sup> Therefore, it is estimated that in TASTE-2, this proportion in the interventional group will be approximately 54% and 45% in the control group. Based on these assumptions, an estimated total sample size of 1362 patients (with a dropout rate

**Table 1** The assessment flow chart

	Baseline	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4
Procedure/ investigation	Before randomisation	The day of randomisation	1st day after randomisation (24±12 hours )	14th day after randomisation or at discharge*	90±7th day after randomisation
Acquiring informed consent	x				
Demographic information			x		
Medical history	x				
Prior medication	x				
Physical examination	x		x	x	x
NIHSS	x		x	x	
mRS	X†			x	x
ECG	x				
Laboratory test	X‡				
Urine pregnancy test	x				
Non-contrast CT/ DWI (ADC)	x		x		
CTA/MRA/DSA	x§				
CTP/MRP	x¶				
Inclusion/ exclusion criteria check	x				
Randomisation		x			
Blood sample		x		x	
Drug delivery		x**			
EVT		x			
Medication adherence				x	
AE/SAE		x	x	x	x
Concomitant medication				x	x

\*If patient has not been discharged on the 14th day after randomisation, record the information on day 14th, if discharged before the day, record the information on the day of discharge. The interventional drug treatment duration is at least 10 days, so the discharge day should not be earlier than the 10th day after randomisation.

†Indicates the prior stroke modified Rankin Scale.

‡Includes blood routine test, blood biochemistry (at least ALT, AST, serum creatinine/estimated glomerular filtration rate, fast glucose, electrolytes) and coagulation profile.

§At least one categories of angiography (CTA or MRA or DSA) was performed at baseline to certify the location of large vessel occlusion in the anterior circulation.

¶For patients within 6–16 hours of symptom onset, the baseline screening image should contain CT+CTA+CTP or DWI+ADC+MRA+MRP (based on the DEFUSE-3 criteria: an infarct core <70 mL, a mismatch volume >15 mL and a mismatch ratio >1.8). For those within 16–24 hours of symptom onset, it should contain CT+CTA+CTP, or DWI+ADC+MRA (based on the DAWN criteria: an NIHSS score ≥10 with an infarct core volume <31 cm<sup>3</sup>, or an NIHSS score ≥20 with an infarct core volume ≤51 cm<sup>3</sup>). CT perfusion or MR diffusion and perfusion scans were evaluated by using an automatic software.

\*\*Interventional drugs should be delivered after randomisation but ahead of EVT.

ADC, apparent diffusion coefficient; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; CTA, CT angiography; CTP, CT perfusion; DSA, digital subtraction angiography; DWI, diffusion-weighted imaging; EVT, endovascular therapy; MRA, MR angiography; MRP, MR perfusion; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SAE, serious AE.

of 5%) and an equal distribution of 681 patients per group will provide at least a power of 90% to detect superiority of edaravone dextroboresol over placebo in improving neurological function at a two-sided alpha significance level of  $p=0.05$ .

### Interim analysis

Given the safety report of edaravone dextroboresol in clinical studies<sup>19 26</sup> as well as the anticipated pace of trial inclusion in China, this study will not conduct interim analyses.

### Statistical analyses

The primary efficacy evaluation will be conducted based on an intention-to-treat analysis, while the analysis of safety will use the safety dataset. Differences in the proportion of mRS 0–2 at 90-day between study groups will be assessed through a logistic regression model, with trial centres considered as a random effect. The results will be presented as OR with a 95% CI. Additionally, we will examine whether the treatment effects vary across predefined subgroups by testing the interaction effect between treatment and subgroup using logistic regression models. Similar strategies to those used for analysing the primary outcome will be applied to other categorical outcomes. For shift analysis, an ordinal logistic regression model will calculate a common OR along with its 95% CI for the ordinal 90-day mRS score. All hypothesis tests will adopt a two-sided alpha level of significant set at 0.05 ( $\alpha=0.05$ ).

A prespecified subgroup analysis will be conducted to assess heterogeneity of treatment effect, with subgroups defined based on the following variables: gender (male or female), age ( $\leq 65$  or  $>65$ ), medical history (hypertension, hypercholesterolaemia, diabetes mellitus, stroke and coronary heart disease status, separately) (yes or no), time interval between last known well and randomisation ( $\leq 6$  hours or  $>6$  hours), NIHSS score range (6–15 or  $>15$ ), ASPECTS score range (8–10 or 6–7), mismatch (yes or no), bridging therapy administration before EVT procedure (with alteplase or without alteplase), location of LVO site within the intracranial internal carotid artery versus M1 segment of middle cerebral artery, and reperfusion status of occluded vessels after EVT procedure according to eTICI scale categories 2b–3 vs 0–2 a.

The statistical analyses will be conducted by using SAS V.9. 4 or a higher version of the statistical software, in accordance with a predetermined statistical analysis plan that we will provide before the database is unmasked and locked.

### Study organisation

This study will be carried out within approximately a hundred centres around mainland China from February 2022 and last about 24 months. To control centre effect, each centre must be experienced in

EVT and has performed at least 50 thrombectomy therapies in the past calendar year and the median door-to-puncture time must be  $\leq 120$  min. During the study, an exit mechanism will be performed. All patients included will be observed to check their reactions to the treatment and can withdraw the informed content at any time for any reason based on the principles of Good Clinical Practice. Responsibility for the trial's organisation lies with the executive and steering committees. The executive committee, led by the principal investigator and assisted by the steering committee, will supervise all the trial activities including protocol development and amendment during the study period. The executive committee is situated at the TASTE-2 Trial Coordinating Centre, which is part of the China National Clinical Research Centre for Neurological Diseases. Meanwhile, the steering committee will consist of recognised experts in neurology and statistics, providing professional supervision and strategic advice. The committee is scheduled to convene semiannually. Trained assessors, who are unaware of the treatment assignment, will adjudicate outcomes, SAEs and brain imaging.

### Version modification

The protocol V.1.0 underwent a minor modification, resulting in the current version being 1.1. In this updated version, we included shift analysis of mRS at 90 days as an additional measure of secondary efficacy outcome without any disruption or impact on the trial's executive processes.

### DISCUSSION

TASTE-2 will address a significant challenge in providing cytoprotection during in-hospital prethrombectomy for AIS patients in the new era of reperfusion therapy. The rationale and design of this study are based on multiple preclinical and clinical studies, adhering to the STAIR recommendations.<sup>4–6</sup> The two primary reperfusion treatments for brain ischaemia, namely thrombolysis and mechanical thrombectomy therapy, have the potential to yield favourable functional outcomes for patients by fully or partially restoring the blood flow within a suitable time window. However, considering the pathophysiology of recanalised blood flow, it may be worth exploring the use of a multitarget cytoprotectant as a viable intervention to mitigate subsequent injury caused by ischaemia and reperfusion.

Recently, the publication of the efficacy and safety of nerinetide for the treatment of AIS (ESCAPE-NA1) trial demonstrated that nerinetide, a postsynaptic density protein 95, did not improve functional outcomes for patients undergoing EVT when compared with placebo.<sup>27</sup> The lack of positive outcome could potentially be explained by the plasmin-mediated enzymatic

breakdown of nerinetide within the alteplase layer. In our search on PubMed and Web of Science for this trial design, we found no evidence suggesting edaravone dextrorotatory is affected by alteplase; however, experimental thrombolysis models indicate edaravone can accelerate thrombolysis with alteplase.<sup>9</sup> Therefore, patients with alteplase are not prohibited and the subgroup analysis of efficacy for patients with or without alteplase before EVT will be performed in this trial. Although DL-3-n-Butylphthalide, a new cytoprotectant, was demonstrated to be efficacious in improving functional outcome for patients with AIS receiving reperfusion therapy, the specific molecular mechanism of action of butylphthalide was unknown and the rate of EVT was rather low.<sup>28</sup> An ongoing phase-III trial of a sublingual tablet containing edaravone dextrorotatory was designed to evaluate its efficacy and safety in terms of functional outcomes in AIS patients. However, the trial excluded patients undergoing EVT.<sup>29</sup>

In conclusion, TASTE-2 represents the pioneering phase-III trial designed to evaluate the efficacy and safety of edaravone dextrorotatory in AIS patients undergoing EVT. This study will generate robust data regarding the effectiveness of this cytoprotective drug in individuals receiving reperfusion treatment.

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**Contributors** CW drafted the manuscript, CW, H-QG, QD, AX, NW, YY, FW and YW contributed to the study design and H-QG contributed to statistical analysis. All authors contributed to critical revision of the manuscript for important intellectual content. YW is the guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the Central Institutional Review Board at Beijing Tiantan Hospital, Capital Medical University (KY2021-177-01). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.

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#### REFERENCES

- Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
- Tymianski M. Combining neuroprotection with endovascular treatment of acute stroke: is there hope *Stroke* 2017;48:1700–5.
- Savitz SI, Fisher M. Future of Neuroprotection for acute stroke: in the aftermath of the saint trials. *Ann Neurol* 2007;61:396–402.
- Savitz SI, Baron J-C, Fisher M, et al. Stroke treatment academic industry roundtable X: brain cytoprotection therapies in the reperfusion era. *Stroke* 2019;50:1026–31.
- Lyden PD. Cerebroprotection for acute ischemic stroke: looking ahead. *Stroke* 2021;52:3033–44.
- Lyden P, Buchan A, Boltze J, et al. Top priorities for cerebroprotective studies—a paradigm shift: report from stair XI. *Stroke* 2021;52:3063–71.
- Zhang N, Komine-Kobayashi M, Tanaka R, et al. Edaravone reduces early accumulation of oxidative products and sequential inflammatory responses after transient focal ischemia in mice. *Stroke* 2005;36:2220–5.
- Wu S, Sena E, Egan K, et al. Edaravone improves functional and structural outcomes in animal models of focal cerebral ischemia: a systematic review. *Int J Stroke* 2014;9:101–6.
- Yamashita T, Sato T, Sakamoto K, et al. The free-radical scavenger edaravone accelerates thrombolysis with alteplase in an experimental thrombolysis model. *Thromb Res* 2015;135:1209–13.
- Enomoto M, Endo A, Yatsushige H, et al. Clinical effects of early edaravone use in acute ischemic stroke patients treated by endovascular reperfusion therapy. *Stroke* 2019;50:652–8.
- Li Y, Ren M, Wang J, et al. Progress in borneol intervention for ischemic stroke: a systematic review. *Front Pharmacol* 2021;12:606682.
- Liu R, Zhang L, Lan X, et al. Protection by Borneol on cortical neurons against oxygen-glucose deprivation/reperfusion: involvement of anti-oxidation and anti-inflammation through nuclear transcription factor kappaB signaling pathway. *Neuroscience* 2011;176:408–19.
- Ma R, Lu D, Xie Q, et al. L-borneol and D-borneol promote transdifferentiation of astrocytes into neurons in rats by regulating WNT/notch pathway to exert neuroprotective effect during recovery from cerebral ischaemia. *Phytomedicine* 2023;109:154583.
- Li J, Zhang L, Xu C, et al. A pain killer without analgesic tolerance designed by co-targeting Ptd-95-Nnos interaction and A2-containing gaba(A)Rs. *Theranostics* 2021;11:5970–85.
- Wu H-Y, Tang Y, Gao L-Y, et al. The synergistic effect of edaravone and borneol in the rat model of ischemic stroke. *Eur J Pharmacol* 2014;740:522–31.
- Hu R, Liang J, Ding L, et al. Edaravone dextrorotatory provides neuroprotective benefits by suppressing Nlrp3 inflammasome-induced microglial pyroptosis in experimental ischemic stroke. *Int Immunopharmacol* 2022;113(Pt A):109315.
- Xu L, Gao Y, Hu M, et al. Edaravone Dextrorotatory protects cerebral ischemia reperfusion injury through activating Nrf2/Ho-1 signaling pathway in mice. *Fundam Clin Pharmacol* 2022;36:790–800.

- 10.1111/fcp.12782 Available: <https://onlinelibrary.wiley.com/toc/14728206/36/5>
- 18 Liu W, Wang L, Liu C, *et al.* Edaravone ameliorates cerebral ischemia-reperfusion injury by downregulating ferroptosis via the Nrf2/Fpn pathway in rats. *Biological & Pharmaceutical Bulletin* 2022;45:1269–75.
  - 19 Xu J, Wang A, Meng X, *et al.* Edaravone dexborneol versus edaravone alone for the treatment of acute ischemic stroke: a phase III, randomized, double-blind, comparative trial. *Stroke* 2021;52:772–80.
  - 20 Albers GW, Marks MP, Kemp S, *et al.* Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708–18.
  - 21 Nogueira RG, Jadhav AP, Haussen DC, *et al.* Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11–21.
  - 22 Xiong Y, Luo Y, Wang M, *et al.* Evaluation of diffusion-perfusion mismatch in acute ischemic stroke with a new automated perfusion-weighted imaging software: a retrospective study. *Neurol Ther* 2022;11:1777–88.
  - 23 Zaidat OO, Yoo AJ, Khatri P, *et al.* Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650–63.
  - 24 Saver JL, Chaisinanunkul N, Campbell BCV, *et al.* Standardized nomenclature for modified rankin scale global disability outcomes: consensus recommendations from stroke therapy academic industry roundtable XI. *Stroke* 2021;52:3054–62.
  - 25 Jia B, Ren Z, Mokin M, *et al.* Current status of endovascular treatment for acute large vessel occlusion in China: a real-world nationwide registry. *Stroke* 2021;52:1203–12.
  - 26 Xu J, Wang Y, Wang A, *et al.* Safety and efficacy of edaravone dexborneol versus edaravone for patients with acute ischaemic stroke: a phase II, Multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial. *Stroke Vasc Neurol* 2019;4:109–14.
  - 27 Hill MD, Goyal M, Menon BK, *et al.* Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (escape-Na1): a multicentre, double-blind, randomised controlled trial. *Lancet* 2020;395:878–87.
  - 28 Wang A, Jia B, Zhang X, *et al.* Efficacy and safety of butylphthalide in patients with acute ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2023;80:851–9.
  - 29 Fu Y, Tang R, Chen R, *et al.* Efficacy and safety of Y-2 sublingual tablet for patients with acute ischaemic stroke: protocol of a phase III randomised double-blind placebo-controlled multicentre trial. *Stroke Vasc Neurol* 2023;svn-2022-002014.