


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

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ABSTRACT

Background and purpose Clinical studies have demonstrated that edaravone dextroboenol can improve the functional outcomes in patients with acute ischaemic stroke (AIS). The present clinical trial aimed at testing the efficacy and safety of Y-2 sublingual tablet on 90-day functional outcome in patients with AIS.

Methods and design This is a randomised, double-blind, placebo-controlled, multicentre, parallel-group trial of Y-2 sublingual tablet on patients with AIS.

An estimated 914 patients at age of 18–80 years with AIS within 48 hours after symptom onset from 40 hospitals will be randomly assigned to receive Y-2 sublingual tablet or placebo for 14 days. Patients are at score 6–20 points on National Institutes of Health Stroke Scale (NIHSS) and had a modified Rankin Scale (mRS) ≤ 1 before this stroke, except mechanical thrombectomy and neuroprotective agents treatment.

Study outcomes The primary outcome is the proportion of patients with mRS ≤ 1 on day 90 after randomisation. Secondary efficacy outcomes include mRS score on day 90, the proportion of patients with mRS ≤ 2 on day 90; the change of NIHSS score from baseline to day 14 and the proportion of patients with NIHSS score ≤ 1 at the days 14, 30 and 90.

Discussion This trial will provide valuable evidence for the efficacy and safety of Y-2 sublingual tablet for improving 90 days the functional outcomes in patients with AIS.

Trial registration number NCT04950920.

INTRODUCTION AND RATIONAL

Although stroke is largely preventable, stroke has remained the second greatest cause of death and the third most common cause of disability, accounting for 6.55 million death and 143 million disability-adjusted life-years in 2019.¹ As a result stroke has posed major health and social economic cost over the world, particularly in low-income and middle-income nations.^{1–3} The key aim of acute stroke treatment is to recanalise occluded vessels early, salvage ischaemic penumbra or volume of hypoperfused, non-functional,

but still salvageable tissue surrounding the infarcted core.¹⁴

Although recombinant tissue-plasminogen activator and endovascular therapy are the major effective approaches for early reperfusion and can achieve good functional outcomes in patients with acute ischaemic stroke (AIS),^{5,6} only a small percentage of patients may benefit from thrombolysis. Neuroprotection approaches suggest that an intervention that modifies the key aspects of the ischaemic cascade can stop ischaemic brain damage from progressing into infarction. However, so far, neuroprotective agents have not been developed for early reperfusion, and the efficacy of neuroprotective drugs have not been established and accepted by most international guidelines.⁷

Several hundred phase 2 studies and many randomised controlled trials of neuroprotective drugs have failed to demonstrate adequate therapeutic efficacy, making the continued search for effective treatments imperative. We hypothesised that one of the most important reasons for the failure of previous studies was that a single neuroprotective entity was not sufficient to achieve significant clinical outcomes.⁸

Edaravone is an effective free radical scavenger and has been recommended for AIS therapy by guidelines for stroke care in China and Japan.^{9,10} Previous studies have demonstrated that edaravone could prevent neuronal and endothelial cell injury in ischaemic stroke following a chain reaction induced by excessive Ca²⁺ influx reactive oxygen species (ROS). This was achieved through inhibiting neurotoxicity, chronic inflammation and modulating the expression of endothelial and neuronal proteins.^{11–13} In addition, preclinical studies demonstrated the effective function of dextroboenol in the

prevention and treatment of nerve injury in ischaemic stroke through multiple mechanisms in ischaemia/reperfusion injury, such as reducing ROS generation, inhibiting nitric oxide (NO) and NO synthase pathways, restraining inflammatory process and caspase-related apoptosis.^{14–17} Dexborneol has also allowed other agents to easily pass through the blood–brain barrier with high permeability to exert therapeutic effects.^{14 16} Edaravone dexborneol is a novel neuroprotective agent that is composed of edaravone and dexborneol. A preclinical trial showed that edaravone dexborneol has a synergistic effect and is more effective in protecting brain from ischaemic and/or ischaemic reperfusion injury than edaravone alone.¹⁷ Furthermore, compared with edaravone, edaravone dexborneol could improve the function outcomes at day 90 in patients with AIS.^{18 19}

Administering drugs intravenously presents a significant challenge in terms of healthcare resources such as beds, nurses, equipment, etc. This could potentially cause delays or limitations in treatment during busy periods, ultimately posing a barrier to protecting neuronal function due to time delays. Y-2 sublingual tablet is an innovative drug, composed of edaravone and dexborneol in a 5:1 ratio (edaravone 30 mg, dexborneol 6 mg). Pharmacokinetic studies have showed that the sublingual formulation is rapidly permeated and absorbed across the buccal membrane without interfering with the disposition and elimination properties, and without significantly altering the total bioavailability of edaravone and dexborneol. Consequently, the peak plasma concentration time (T_{max}), peak plasma concentration (C_{max}) and the area under the curve (AUC) remain largely unchanged.

In animal and human experiments, the pharmacokinetics parameters (C_{max} , AUC_{0-t} , AUC_{0-inf} , $t_{1/2}$, MRT) of intravenous and oral edaravone dexborneol are similar. Data in animal experiments using edaravone demonstrated the following results: AUC, 5290 hours \times ng/mL in animals compared with 5900 hours \times ng/mL in humans, C_{max} : 2110 ng/mL in animals compared with 2436 ng/mL in humans. The following results were demonstrated using dexborneol: AUC: 30.8 ng/mL in animals compared with 23.8 hours \times ng/mL in humans, C_{max} 20 ng/mL in animals compared with 33 ng/mL in human.²⁰

The objective of this multicentre, randomised, double-blind, comparative phase III trial is to evaluate the safety and effective of edaravone dexborneol sublingual tablet in patients with AIS.

METHODS

Design

In this multicentre, randomised, double-blind and placebo-controlled, phase III trial, eligible patients will be randomly assigned to one of the two treatment groups (Y-2 sublingual tablet or Y-2 sublingual tablet placebo) in a 1:1 ratio within 48 hours of the onset of symptoms of AIS and followed up for 90 days after randomisation.

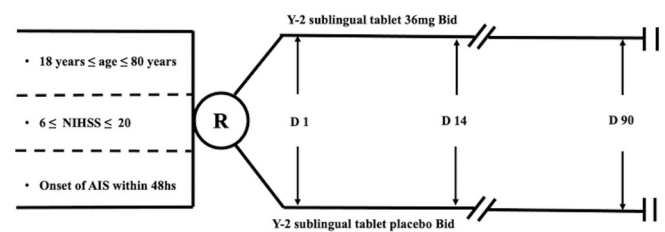


Figure 1 Flow chart of the Y-2 sublingual tablet for treatment of acute ischaemic stroke (AIS) trial. NIHSS, National Institutes of Health Stroke Scale.

The study design and visit plan are shown in [figure 1](#) and [table 1](#). The trial is designed according to the principles of the Declaration of Helsinki.

All patients or the patient’s legal representative will be asked to provide informed consent. An international, independent data and safety monitoring board will be in charge of overseeing the study’s conduct, safety and efficacy. The study was prospectively registered on ClinicalTrials.gov (NCT04950920).

The study will run in 40 large hospitals in China for a total period of 2 years with 1 year of patient recruitment. The first patient will be enrolled on 28 June 2021, and the estimated last patient will be enrolled on June 2022.

Patient population

The trial will enrol subjects aged between 18 and 80 years old, who have a clinical diagnosis of AIS within 48 hours of stroke onset, have a baseline NIHSS score between 6 and 20, a total score of upper and lower limbs on motor deficits ≥ 2 , and an mRS score ≤ 1 before this stroke. Intravenous thrombolysis is allowed in the study, but endovascular therapy is not allowed. The patients can receive appropriate standard stroke care in accordance with regional treatment practice, except mechanical thrombectomy and treatment with neuroprotective agents. The comprehensive inclusion and exclusion criteria are shown in [box 1](#).

Blinding and randomisation

This trial is double-blind, the patient and all those involved in the clinical outcomes and the assessment of outcomes will be blinded to the treatment group. To ensure that the approximate balance allocation is in a 1:1 ratio, the randomisation will be stratified by clinical centres including the time onset of AIS (≤ 24 hours or >24 hours). In each stratum, eligible patients will be randomly assigned to the Y-2 sublingual tablet group or the Y-2 sublingual tablet placebo group. A table for the allocation to the treatment group will be prepared by the statistical team and will not be available to the investigators. The random number list will be created centrally using SAS V.9.4 by a separate statistician. Following randomised allocation, the study treatment intervention for the patient will take place as early as possible.

Table 1 Visit plan

Measures	Baseline	Treatment			Follow-up	
		Day 0	Day 7±1	Day 14±3	Day 30±7	Day 90±7
Informed consent	X					
Demographics	X					
History of illness	X					
Medical history	X					
Prior medication						
Inclusion and exclusion criteria	X					
Vital signs and physical examination	X		X	X	X	X
NIHSS	X			X	X	X
mRS	X*			X	X	X
Head CT/MRI†	X					
Laboratory examination‡	X		X	X	X	X
Electrocardiograph	X		X	X	X	X
Randomisation	X					
Administration						
TOAST classification		X				
Pregnancy tests§	X					
Biomarkers¶	X		X	X		
Compliance						
Concomitant medication	X	X	X	X	X	X
AE/SAE		X	X	X	X	X

*Pre acute ischaemic stroke onset.
†The baseline imaging, whatever CT or MRI, is used to exclude intracranial haemorrhage. Imaging data from another hospital is accepted according to investigators.
‡Including blood routine examination, urinalysis, blood glucose, renal function, liver function, coagulation profile, myocardial zymogram, lipid profile, homocysteine.
§Pregnancy test is limited to female subjects of childbearing age.
¶Including interleukin 6, interleukin 1 β , tumour necrosis factor α , matrix metalloproteinase 9, brain derived neurotrophic factor and intracellular adhesion molecule-1.
AE, adverse event; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SAE, serious AE; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Treatment

Y-2 sublingual tablet or Y-2 sublingual tablet placebo will be distributed in prerandomised and the sealed treatment packs are externally indistinguishable. After randomisation, the eligible patients are randomly assigned to one of two treatments:

Y-2 sublingual tablet group: Y-2 sublingual tablet, 36 mg (edaravone 30 mg, dexborneol: 6 mg), twice a day, for a treatment cycle 14 days.

Y-2 sublingual tablet placebo group: Y-2 sublingual tablet placebo (edaravone 0 mg, dexborneol: 60 μ g), twice a day, for a treatment cycle 14 days.

The study period refers to the period from randomisation to day 90 of treatment or last follow-up.

Efficacy outcome assessment

The primary efficacy outcome is the proportion of patients with an excellent functional outcome, defined as a score of 0–1 on the mRS at day 90 after randomisation.

The mRS is a global measure of disability or dependence in daily activities, composed of seven grades ranging from 0 (no symptoms) to 6 (death).

The secondary efficacy outcomes are mRS score on day 90, the proportion of patients achieving a good functional outcome (mRS \leq 2) on day 90, the change of NIHSS score from baseline to 14 days and the proportion of patients achieving NIHSS score \leq 1 on day 14, 30 and 90 after randomisation.

Safety outcome assessment

The safety endpoints included adverse events, treatment-related adverse events within 90 days and changes in vital signs and laboratory data before and after treatment.

Data safety and monitoring board

This trial has an independent data monitoring committee (IDMC) which is independent of the researchers and the steering committee. IDMC will monitor the safety

Box 1 Inclusion and exclusion criteria
Inclusion criteria

1. Aged from 18 to 80 years old, male or female.
2. Baseline National Institutes of Health Stroke Scale (NIHSS) score between 6 and 20, a total score of the upper limb and the lower limb ≥ 2 at admission.
3. Acute ischaemic stroke symptom onset within 48 hours, onset time defined as when patient was last known to be well.
4. According to the 'Diagnostic criteria of cerebrovascular diseases in China (version 2019)', patients were diagnosed with ischaemic stroke, with their first onset or recovered well after the last onset (modified Rankin Scale score ≤ 1 before this onset).
5. Informed consent from the patient or legally authorised representative.

Exclusion criteria

1. Intracranial bleeding disorders which were confirmed by cranial CT scan, including haemorrhagic stroke, epidural haematoma, intracranial haematoma, intraventricular haemorrhage, subarachnoid haemorrhage, etc.
2. Severe disturbance of consciousness: NIHSS category 1a for consciousness > 1 .
3. Transient ischaemic attack.
4. Systolic blood pressure ≥ 220 mm Hg or diastolic blood pressure ≥ 120 mm Hg after blood pressure control.
5. Severe mental disorder and dementia.
6. Alanine aminotransferase or aspartate transaminase $> 2.0 \times$ upper limit of normal value (ULN) or with known liver disorder, such as acute hepatitis, chronic active hepatitis, hepatic cirrhosis, etc.
7. Known kidney disease, renal insufficiency, serum creatinine $> 1.5 \times$ ULN or creatinine clearance < 50 mL/min.
8. Received neuroprotective agents after this onset, including commercially available edaravone, edaravone dexborneol injection, nimodipine, ganglioside, citicoline, piracetam, butylphthalide and urinary kallidinogenase, etc.
9. Received or planned embolectomy or interventional therapy after this onset.
10. Concurrent malignant tumour or currently receive antitumour treatment.
11. Severe systemic disease and life expectancy < 90 days.
12. Allergies to edaravone, (+)-borneol, or the excipients.
13. Pregnant or lactating patients or patients who plan to become pregnant.
14. History of a major surgery within 4 weeks before enrolment.
15. Participated in other clinical trials within 30 days before randomisation or currently involved in other clinical trials.
16. Investigators consider they are not suitable for this trial.

and efficacy data gathered during the study, including serious unexpected adverse events, unnecessary risks. Interim analyses will be conducted when 50% of subjects completed follow-up at 90 days. If the event of unexpected safety concerns or treatment differences were apparent at the interim analyses which was performed by an independent statistician, the IDMC should provide professional advice to the steering committee or recommend terminate the trial.

Sample size

The primary efficacy outcome is the proportion of patients achieving an mRS ≤ 1 at 90 days. According to TASTE

trial (Treatment of Acute Ischemic Stroke with Edaravone Dexborneol),¹⁸ the proportion of patients with an mRS score of ≤ 1 on day 90 is 50% in the experimental group and 40% in the control group. Taking a two-sided α of 0.05 and a power of 80%, the required sample size for each group is 388. Considering a drop-out rate of 15%, a total sample size of 914 are estimated with 457 patients per group.

Interim analysis

The primary goal of the interim analysis is to evaluate primary efficacy and re-estimate the sample size. An interim analysis will be done when half of all patients have finished the follow-up at day 90. The sample size will be maximumly increased up to 1.5 times from the originally planned sample size and will not decrease. The sample size re-estimation will be estimated according to conditional power calculations as indicated by the promising zone method. To manage the overall type I error = 0.025 (one-sided), the significance level will be adjusted. If the sample size was adjusted, the final statistical analysis of the primary efficacy outcome and the correction of p value will be performed based on the Cui, Hung, Wang approach using a weighted statistic.²¹ The IDMC will conduct interim analysis.

Statistical analyses

An intention-to-treat analysis will be performed for statistical analysis. For baseline characteristics, continuous variables will be provided as the mean \pm SD or median with IQR and compared using a t-test or a Wilcoxon sum of rank test. Categorical variables will be provided as numbers with percentage and will be compared using either the χ^2 test or the Fisher's exact test.

For the primary efficacy outcome, the group difference will be conducted using the χ^2 test, and the corresponding 95% CIs between the proportion will be estimated based on the normal approximation. The OR and 95% CI for mRS score of 0–1 on day 90 after randomisation will be calculated using logistic regression.

For secondary efficacy outcomes, binary outcomes will be analysed with a similar approach as for the primary efficacy outcome. The mRS scores on day 90 of each group will be compared by ordinal logistic regression, calculated common ORs and the 95% CI. Changes in NIHSS score from baseline to day 14 in each group will be presented as means with 95% CIs and the mean differences between the groups will be estimated by generalised linear regression.

A $p < 0.05$ in two tails is considered statistically significant. Statistical analysis will be performed by using the SAS V.9.4 software.

DISCUSSION

This multicentre, randomised, control trial will assess the efficacy and safety of the Y-2 sublingual tablet, which is composed of edaravone and dexborneol in patients with AIS.



Previous studies have demonstrated intravenous thrombolysis and endovascular treatment are the most effective managements to successful reperfusion in patients suffering from AIS.⁶ However, even after achieving successful recanalisation, there are 41%–55% patients with an unfavourable clinical outcome at day 90, which resulted in futile recanalisation.^{22–24} Delayed onset to puncture and puncture to reperfusion are associated with higher risk of futile recanalisation.^{24–26} So, timely and effective management can improve clinical outcomes and decrease futile recanalisation rates in patients with AIS.

Edaravone dextroborneol is a multitarget neuroprotective drug with both antioxidant and anti-inflammatory effects to improve the outcome of ischaemic stroke through scavenging hydroxyl-free, peroxy-free and superoxide-free radicals, relieving cerebral oedema, with an anti-inflammatory effect and consequently inhibiting delayed neuronal death.^{11 15 27–29} Clinical studies have proven that edaravone dextroborneol injection could improve the functional outcomes in patients with AIS.^{18 19}

Importantly, there are still some differences between the current Y-2 trial and previous study. First of all, the control group of the current trial is a placebo, whereas the control group of a previous injection study is edaravone, which is the active ingredient. Second, Y-2 trial has an increased number of patients receiving intravenous thrombolysis in the subject population and the efficacy of neuroprotective agents in the patient population receiving recanalisation treatment can be further analysed during postanalysis. Third, although the proportion of the Y-2 oral dosage form and injection component is different, the proportion of the Y-2 component is roughly similar to that of injection in terms of bioavailability.

As the Y-2 sublingual tablet is not restricted by healthcare resource (beds, nurse, equipment, etc), it can be administrated easily and earlier to AIS patients. This is significant as a trend has been found in previous studies, that patients can receive more benefit from an earlier treatment window.

Y-2 sublingual tablet is the first sublingual tablet to be administrated in patients with AIS. The randomised, multicentre and prospective design of this study has great methodological superiority to control confounding bias and selection bias. In addition, the scientific calculation of the sample size guarantee strong statistical power and the results will be statistically reliable.

SUMMARY AND CONCLUSION

This randomised, double-blind, placebo-controlled, multicentre trial will produce reliable data on the efficacy and safety of the Y-2 sublingual tablet in patients with AIS. Using the sublingual tablet as a new method of treatment will provide timely intervention and improve the clinical outcomes for patients who had a stroke.

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Competing interests RT, JR, SZ and XF are the employees of Sincere Pharmaceutical Group; RC is the employee of Neurodawn Pharmaceutical. Those companies have developed the drug and sponsored the trial. The above-mentioned five authors from companies provided information on the pharmacological mechanism of drugs, gave preclinical experimental data and advised on study design. No other competing interests were reported.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and ethics approval was approved by Institutional Review Board of Peking University Third Hospital with number D2020185. 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. No data are available.

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