

# Safety and efficacy of compound edaravone versus edaravone for patients with acute ischaemic stroke: a phase II, multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial

Jie Xu,<sup>1,2</sup> Yilong Wang,<sup>1,2</sup> Anxin Wang,<sup>1,2</sup> Zhiqiang Gao,<sup>3</sup> Xiaoping Gao,<sup>4</sup> Huisheng Chen,<sup>5</sup> Junshan Zhou,<sup>6</sup> Xingquan Zhao,<sup>1,2</sup> Yongjun Wang<sup>1,2</sup>

**To cite:** Xu J, Wang Y, Wang A, et al. Safety and efficacy of compound edaravone versus edaravone for patients with acute ischaemic stroke: a phase II, multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial. *Stroke and Vascular Neurology* 2019;0:e000221. doi:10.1136/svn-2018-000221

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/svn-2018-000221>).

JX, YW and YW contributed equally.

Received 29 December 2018  
Revised 20 February 2019  
Accepted 25 February 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Prof. Xingquan Zhao;  
zxq@vip.163.com and  
Dr Yongjun Wang;  
yongjunwang@ncrcnd.org.cn

## ABSTRACT

**Background** Compound edaravone is a novel neuroprotective agent that comprised edaravone and (+)-borneol, a food additive with an anti-inflammatory effect in animal ischaemic stroke models. This study aims to assess the safety and efficacy of compound edaravone compared with edaravone in treating patients with acute ischaemic stroke (AIS).

**Methods** In this multicentre, randomised, double-blind, multiple-dose, active-controlled, phase II clinical trial, patients with AIS within 48 hours after stroke onset were randomly assigned (1:1:1:1) to low-dose (12.5 mg), medium-dose (37.5 mg) or high-dose (62.5 mg) compound edaravone groups, and an active control group with edaravone (30 mg) by 30 min intravenous infusion every 12 hours, for 14 consecutive days. The primary efficacy outcome was the proportion of modified Rankin Scale (mRS) score  $\leq 1$  at 90 days and National Institutes of Health Stroke Scale (NIHSS) score change from baseline to 14 days after randomisation. The safety outcome included any adverse event during 90 days after treatment.

**Results** Of 385 patients included in the efficacy analysis, 94 were randomised to low-dose group, 97 to medium-dose group, 98 to high-dose group and 96 to the control group. No significant difference was observed among the four groups on mRS score (mRS  $\leq 1$ ,  $p=0.4054$ ) at 90 days or NIHSS score change at 14 days ( $p=0.6799$ ). However, a numerically higher percentage of patients with mRS score  $\leq 1$  at 90 days in the medium-dose (69.39%) and high-dose (65.63%) groups was observed than in the control group (60.64%). No significant difference in severe adverse events was found among the four groups ( $p=0.3815$ ).

**Conclusions** Compared with edaravone alone, compound edaravone was safe and well tolerated at all doses, although no significant improvement in functional outcomes was observed at 90 days.

**Trial registration number** NCT01929096.

## INTRODUCTION

Stroke is the leading cause of death and acquired adult disability in China and has significant economic burden.<sup>1 2</sup> However, numerous neuroprotective agents have failed to show any benefit in the treatment of patients with acute ischaemic stroke (AIS), making the search for new treatments imperative.<sup>3</sup> Edaravone is an effective free radical scavenger<sup>4 5</sup> recommended for AIS treatment by Chinese and Japanese stroke care guidelines.<sup>6 7</sup> Edaravone scavenges free radicals, such as hydroxyl free radical ( $\cdot\text{OH}$ ), nitric oxide free radicals ( $\text{NO}\cdot$ ) and peroxynitrite anion ( $\text{ONOO}^-$ ), sequentially relieves cerebral oedema, and inhibits delayed neuronal death.<sup>4 8 9</sup> However, cerebral ischaemic injury is extremely complex and involves free radicals and inflammatory response. (+)-Borneol inhibits the production or expression of inflammation-related proteins and prevents brain injury or impairment. Compound edaravone is a novel neuroprotective agent that comprised edaravone and (+)-borneol in a 4:1 ratio<sup>10</sup> that may have a better therapeutic effect.<sup>11 12</sup> Complementarity exists between edaravone and (+)-2-camphol. Pharmacological research on the efficacy of edaravone combined with (+)-borneol showed that, compared with edaravone alone, compound edaravone showed synergistic effect and longer treatment time, which indicated that the protective effect of compound edaravone on cerebral ischaemic injury was better than that of the marketed edaravone. The present multicentre, randomised, active-controlled, double-blind study aims to verify the safety

and efficacy of compound edaravone in patients with AIS.

## METHODS

### Study design

This was designed as a phase II, multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial conducted at 28 centres in China between May 2013 and February 2015. Patients were assigned to treatment after they had given informed consent.

### Patient selection

Patients who met the following inclusion criteria were eligible for enrolment: age 35–75 years, diagnosis of AIS, ability to start the study drug within 48 hours after stroke onset, a National Institutes of Health Stroke Scale (NIHSS) score between 4 and 24, and a total score of upper and lower limbs  $\geq 2$  on motor deficits.

### Study intervention

For this trial, 400 cases were planned to be randomised into four groups: control group (edaravone injection, 30 mg/dose, once every 12 hours, continued for 14 days), low-dose group (compound edaravone injection, 12.5 mg/dose [edaravone 10 mg, (+)-borneol 2.5 mg], one dose every 12 hours, continued for 14 days), medium-dose group (compound edaravone injection, 37.5 mg/dose [edaravone 30 mg, (+)-borneol 7.5 mg], one dose every 12 hours, continued for 14 days) and high-dose group (compound edaravone injection, 62.5 mg/dose [edaravone 50 mg, (+)-borneol 12.5 mg], one dose every 12 hours, continued for 14 days). Randomisation was stratified according to the interval between the stroke onset and enrolment ( $\leq 24$  hours vs between 24 hours and 48 hours). The randomisation number was assigned by an automated randomisation system.

### Efficacy outcome assessment

The primary efficacy outcome was defined as the proportion of modified Rankin Scale (mRS) score  $\leq 1$  at 90 days and NIHSS score change from baseline to 14 days after randomisation; the secondary efficacy outcomes included (1) NIHSS score  $\leq 1$  at 14, 30 and 90 days after randomisation; (2) Barthel Index  $\geq 95$  at 14, 30 and 90 days after randomisation; (3) Montreal Cognitive Assessment score at 14, 30 and 90 days after randomisation; and (4) Stroke Impact Scale score at 90 days.

### Safety outcome assessment

Data for safety assessment included adverse reactions observed during the trial and changes in laboratory data before and after treatment. Severe adverse events (SAEs) included disability, prolonged hospitalisation and death.

### Statistical analysis

Based on the principle of intention-to-treat analysis, all randomised patients were included in the safety analysis, and patients who had at least one valid assessment were

included in the efficacy analysis. The last observation was used for patients who withdrew from the study and counted as lack of efficacy. Data for patients who withdrew because of safety or other reasons were included throughout the last visit and before the termination of the study. The baseline characteristics in four groups were compared. Proportions were used for categorical variables, and means with SD were used for continuous variables. Differences in efficacy and safety outcomes among four groups were analysed. Continuous data were analysed by analysis of variance or Kruskal-Wallis test, and categorical data examined by  $\chi^2$  test or Fisher's exact test. All tests were two-sided, and a p value of 0.05 was considered statistically significant. All statistical analyses were performed using SAS V.9.2 software.

## RESULTS

### Baseline characteristics

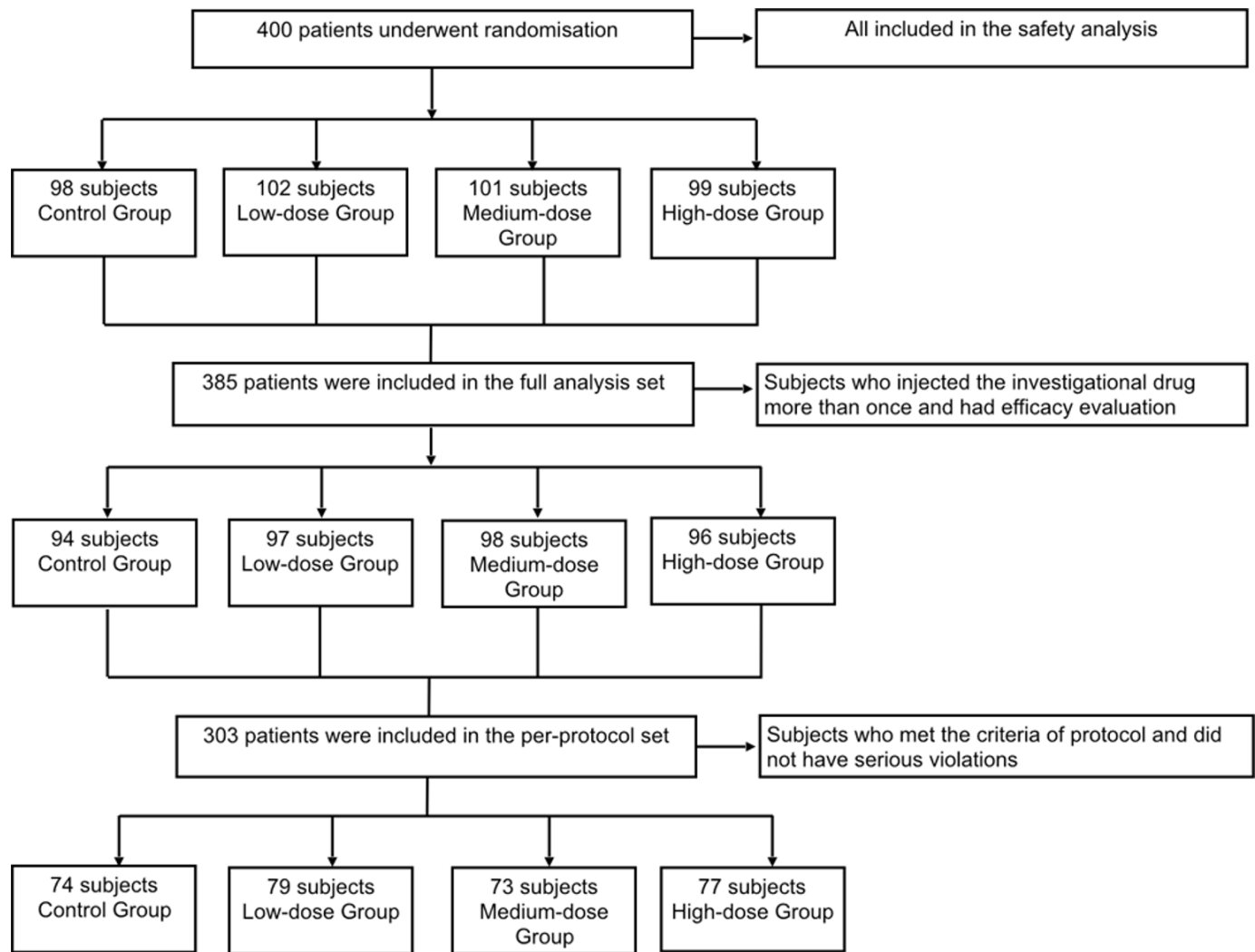
The trial enrolled 400 patients: 98 in the control group, 102 in the low-dose group, 101 in the medium-dose group and 99 in the high-dose group. All received the treatment for the first time and included in the safety analysis. Fifteen patients lost to follow-up before the first assessment were excluded in the efficacy analysis. Of the remaining 385 patients, 303 completed the study according to the protocol (figure 1). Baseline demographic and clinical characteristics were well matched among the four groups analysed based on the efficacy data (table 1).

### Safety analysis

The incidence of adverse reactions was 6.12%, 8.82%, 10.89% and 14.14% in the control, low-dose, medium-dose and high-dose groups, respectively. The details of adverse reactions are listed in online supplementary table 1. The severe adverse reactions leading to withdrawal were observed in 3 (3.06%), 2 (1.96%), 3 (2.97%) and 4 (4.04%) patients in the control, low-dose, medium-dose and high-dose groups, respectively. The major adverse reactions included pruritus, skin rash, acute liver injury and kidney injury. SAEs were observed in 10 (10.20%), 4 (3.92%), 6 (5.94%) and 7 (7.07%) patients in the control, low-dose, medium-dose and high-dose groups, respectively, and no significant difference was found ( $p=0.3815$ ). Among a total of 29 SAEs, 2 events (severe liver and kidney damage) were related to compound edaravone, both of which happened in one patient in the high-dose group. However, recovery was achieved after the treatment. Two patients in the edaravone control group and 0 patient in the compound edaravone group died. These two deaths in the edaravone control group were considered as unrelated to the treatment, and the causes of death were worsening of stroke and septicaemia.

### Efficacy outcomes

The incidence of primary efficacy outcome (mRS scores of  $\leq 1$  after treatment at 90 days) in the control, low-dose, medium-dose and high-dose groups was 60.64%, 58.76%, 69.39% and 65.63%, respectively. No significant difference



**Figure 1** Flow chart of the clinical trial.

was observed ( $p=0.4054$ ). However, the proportion of mRS score of  $\leq 1$  in medium-dose and high-dose groups had possible higher trend than in the control group (69.39% and 65.63% vs 60.64%; [figure 2A](#)). Moreover, no significant difference was seen among the four groups in terms of NIHSS score changes from baseline to 14 days after treatment ( $p=0.6799$ ; [figure 2B](#)). The secondary efficacy outcomes in this trial are summarised in [table 2](#). There were no significant differences among the four groups in terms of these secondary efficacy outcomes.

## DISCUSSION

In this phase II, multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial, compound edaravone at different doses was compared with edaravone alone for efficacy and safety. Our result showed that, compared with edaravone alone, compound edaravone was safe and well tolerated at all doses, although no significant improvement in functional outcomes was observed.

Neuroprotective drugs might extend the therapeutic time window after stroke for thrombolysis or thrombectomy therapy by delaying cell death and blocking

reperfusion injury. Compound edaravone could provide as a new and effective treatment of stroke in the future.<sup>13</sup> After onset of ischaemic stroke, several risk factors were associated with the damage process of neurons under ischaemia: energy failure, free radicals production, formation of neurotoxin, inflammatory responses and apoptosis.<sup>14</sup> Although vascular recanalisation could effectively salvage reversible ischaemic tissue,<sup>15</sup> the risk of reperfusion injury was high. Edaravone could limit vascular endothelial cell injury, brain oedema,<sup>16 17</sup> tissue injury<sup>18</sup> and delayed neuronal death, and consequently reduced neurological deficits.<sup>19</sup> Additionally, as seen on sequential magnetic resonance spectroscopy, preservation of N-acetyl-aspartate, a neuron-specific amino acid, in the ischaemic brain of edaravone-treated patients has been reported.<sup>20</sup> Compound edaravone is a novel neuro-protective agent indicated for AIS.<sup>10</sup> It is a compound preparation comprising edaravone and (+)-borneol in a 4:1 ratio. The natural borneol consists of over 96% borneol that could inhibit the production or expression of inflammation-related proteins such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$ , cyclo-oxygenase-2 and

**Table 1** Baseline characteristics (FAS)

Characteristics	Control	Low-dose	Medium-dose	High-dose	P value
n	94	97	98	96	
Age (years)	59.71±8.33	58.13±8.46	59.11±8.95	59.55±9.53	0.6020
≤65, n (%)	67 (71.28)	75 (77.32)	75 (76.53)	68 (70.83)	0.6264
>65, n (%)	29 (28.72)	22 (22.68)	23 (23.47)	28 (29.17)	
Gender, n (%)					
Male	65 (69.15)	67 (69.07)	65 (66.33)	64 (66.67)	0.9606
Female	29 (30.85)	30 (30.93)	33 (33.67)	32 (33.33)	
Weight (kg)					
Male	71.95±10.33	72.13±10.25	74.45±9.77	72.80±10.51	0.4892
Female	62.50±7.99	64.53±9.82	61.48±11.81	60.69±9.36	0.4591
Height (cm)					
Male	169.70±5.10	170.33±5.42	171.00±5.24	170.94±4.28	0.4246
Female	158.69±3.70	159.60±4.75	158.79±4.46	158.09±5.21	0.6397
BMI (kg/m <sup>2</sup> )					
Male	25.00±3.22	24.82±3.15	25.44±3.02	24.88±3.18	0.6763
Female	24.81±3.07	25.31±3.56	24.38±4.73	24.22±3.12	0.6578
Temperature (°C)	36.48±0.31	36.46±0.27	36.47±0.32	36.50±0.32	0.8285
Breath (breaths per minute)	18.32±1.57	18.13±1.74	18.34±1.51	18.75±5.05	0.4913
HR (beats per minute)	74.82±9.51	72.59±10.14	75.92±12.46	74.22±10.21	0.1707
SBP (mm Hg)	150.91±20.93	150.61±24.83	148.91±19.18	149.46±19.59	0.8891
DBP (mm Hg)	88.53±12.26	88.70±13.11	88.43±11.75	88.55±12.84	0.9987
Stroke history, n (%)	25 (26.60)	24 (24.74)	25 (25.51)	27 (28.13)	0.9560
Family stroke history, n (%)	9 (9.57)	7 (7.22)	14 (14.29)	11 (11.46)	0.6241
Hypertension, n (%)	57 (60.64)	64 (65.98)	78 (79.59)	65 (67.71)	0.0315
Hyperlipidaemia, n (%)	4 (4.26)	11 (11.34)	11 (11.22)	8 (8.33)	0.4435
Diabetes, n (%)	21 (22.34)	26 (26.80)	28 (28.57)	24 (25.00)	0.7887
Cardiac disease, n (%)	16 (17.02)	14 (14.43)	19 (19.39)	19 (19.79)	0.7315
Smoking, n (%)	43 (45.74)	47 (48.45)	44 (44.90)	41 (42.71)	0.8842
Heavy alcohol consumption, n (%)	6 (6.38)	10 (10.31)	8 (8.16)	7 (7.29)	0.7981
Obesity, n (%)	42 (45.16)	45 (46.39)	47 (47.96)	42 (43.75)	0.9449
Other comorbidities, n (%)	86 (91.49)	92 (93.81)	95 (96.94)	90 (93.75)	0.4396
NIHSS score at baseline	7.01±3.41	7.23±3.12	6.99±3.31	6.75±2.85	0.6723
mRS before onset, n (%)					
0	81 (86.17)	87 (89.69)	91 (92.86)	86 (89.58)	0.5135
1	13 (13.83)	10 (10.31)	7 (7.14)	10 (10.42)	
Time since stroke onset (hours)	27.57±11.75	29.08±12.16	27.50±12.11	28.05±12.37	0.7595

Continued



Table 1 Continued

Characteristics	Control	Low-dose	Medium-dose	High-dose	P value
BMI, body mass index; DBP, diastolic blood pressure; HR, heart rhythm; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.					test

induced nitric oxide synthase (iNOS), and prevent brain injury or impairment.<sup>11</sup> Borneol has been widely used to treat cerebrovascular disease, but is rarely used alone.<sup>21</sup>

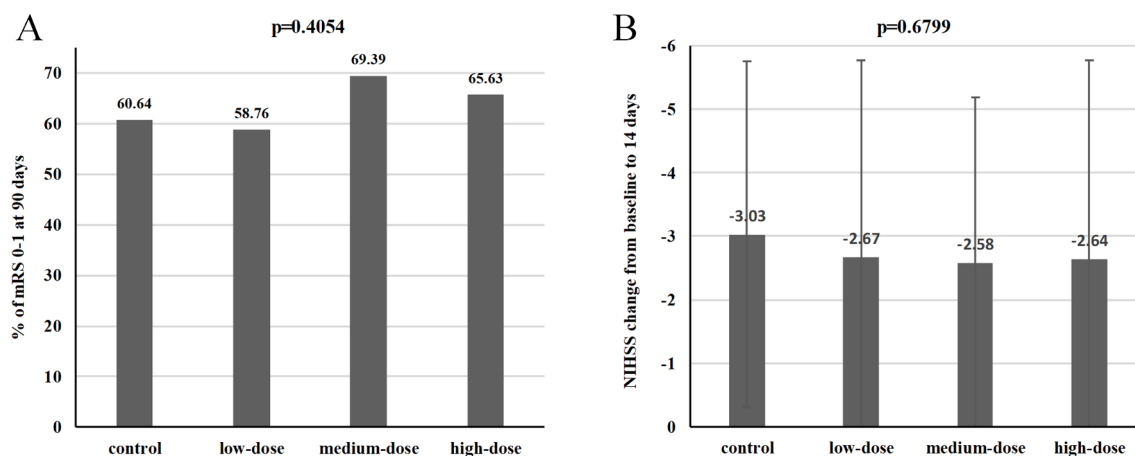
In this trial, the major adverse reactions included pruritus, skin rash, acute liver injury and kidney injury. The adverse reactions of compound edaravone seemed to show a dose-dependent relationship. It is worth noting that, among a total of 29 SAEs, 2 events (severe liver and kidney damage) were related to compound edaravone, both of which happened in one patient in the high-dose group. The underlying pharmacological mechanisms remained unclear. In consideration of safety, high-dose compound edaravone should not be recommended for further clinical investigation.

Although no significant difference was found among the four groups in the primary efficacy outcome, proportions of the patients with mRS score of  $\leq 1$  at 90 days in the group treated with medium-dose (69.39%) or high-dose (65.63%) compound edaravone were higher than in the group treated with edaravone (60.64%), and we found the efficacy of the medium-dose compound edaravone was likely to be even better than the high-dose one. In combination with efficacy and safety data, a phase III clinical trial with the medium-dose edaravone group, with a dose of 37.5 mg/time (edaravone 30 mg, (+)-borneol 7.5 mg) is suggested.

Compound edaravone can improve acute brain injury considerably in animal models of focal cerebral ischaemia (reperfused or permanent) and whole cerebral ischaemia reperfusion.<sup>22</sup> No drug interaction in vivo between edaravone and (+)-borneol was observed from the preclinical pharmacokinetic study, including absorption, distribution, metabolism and excretion. Edaravone and (+)-borneol rapidly distributed in most tissues and

excreted mainly from urine and bile in a conjunction form. Edaravone, (+)-borneol and compound edaravone were not inhibitors or inducers of major CYP (Cytochrome P450 proteins) enzymes (online supplementary table 2). The risk of genetic and reproductive toxicity was not observed in the preclinical studies (online supplementary tables 3 and 4). The pathophysiological mechanism of cerebral ischaemic injury is complex, involving factors such as excitatory amino acids, calcium overload, free radicals, inflammatory response and apoptosis.<sup>18</sup> Pharmacological intervention alone cannot affect this complex process effectively.<sup>9</sup> Studies that engage multiple targets to improve ischaemic injury are ongoing.<sup>23–25</sup> In theory, using two different agents to target different steps of ischaemic injury is likely superior to a single agent in preventing ischaemia.<sup>26</sup>

Compound edaravone enhanced inhibition of iNOS and TNF- $\alpha$  expression and lower level of ONOO<sup>-</sup> in the ischaemic brain. It could contribute to the synergistic effect of edaravone and borneol in combination. However, this study has several limitations. First, since the study is a phase II study and the sample is small, we cannot make further explorations on the effect of compound edaravone on each TOAST (Trial of Org 10 172 in Acute Stroke Treatment) type with stratification analysis, which will be done in the phase III study. Second, for ethical reasons, only a positive control group (edaravone group) was set up in the study and there was no placebo control group. Third, since no blood samples were collected from the patients in the study, we cannot measure the changes in inflammatory factors before and after medication, and inflammatory factors will be used as secondary indicators to analyse the anti-inflammatory effect of compound edaravone.



**Figure 2** Primary efficacy outcomes. (A) % of mRS score 0–1 at 90 days. (B) NIHSS score change from baseline to 14 days. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

**Table 2** Secondary efficacy outcomes among the four groups

Variables	Time (days)	Control n=94	Low-dose n=97	Medium-dose n=98	High-dose n=96	P value
NIHSS score $\leq 1$ , n (%)	14	27 (28.72)	20 (20.62)	20 (20.41)	21 (21.88)	0.4975
	30	32 (35.16)	35 (36.46)	36 (38.30)	37 (38.95)	0.9505
	90	49 (54.44)	49 (51.04)	51 (54.26)	54 (58.06)	0.8180
BI score $\geq 95$ , n (%)	14	40 (42.55)	43 (44.79)	41 (42.27)	44 (45.83)	0.9514
	30	50 (54.35)	48 (50.00)	56 (59.57)	58 (61.05)	0.3994
	90	66 (71.74)	61 (63.54)	68 (71.58)	63 (67.02)	0.5672
MoCA, mean $\pm$ SD	14	21.29 $\pm$ 6.46	20.54 $\pm$ 6.35	22.07 $\pm$ 6.36	20.69 $\pm$ 7.20	0.3325
	30	23.31 $\pm$ 5.75	22.52 $\pm$ 6.35	23.00 $\pm$ 6.34	22.56 $\pm$ 6.80	0.8773
	90	23.99 $\pm$ 5.68	23.67 $\pm$ 5.37	23.53 $\pm$ 6.84	22.56 $\pm$ 6.80	0.7897
SIS, mean $\pm$ SD	90	635.48 $\pm$ 141.91	618.50 $\pm$ 152.51	637.52 $\pm$ 143.67	623.68 $\pm$ 159.71	0.8230

BI, Barthel Index; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; SIS, Stroke Impact Scale.

## CONCLUSION

Medium-dose compound edaravone was safe in this phase II, multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial. However, the efficacy still needs to be explored in a large trial. The medium-dose edaravone group (37.5 mg/time) (edaravone 30 mg, (+)-borneol 7.5 mg) will be the optimal dose for a phase III clinical trial.

## Author affiliations

<sup>1</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

<sup>2</sup>China National Clinical Research Center for Neurological Diseases, Beijing, China

<sup>3</sup>Department of Neurology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China

<sup>4</sup>Department of Neurology, The First Affiliated Hospital of Hunan Normal University, Changsha, China

<sup>5</sup>Department of Neurology, General Hospital, PLA Shenyang Military Region, Shenyang, China

<sup>6</sup>Department of Neurology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

**Contributors** YoW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. XZ and YiW contributed equally to this work. Study concept and design: YoW. Supplying patients: XZ, YiW, ZG, XG, HC and JZ. Drafting of the manuscript: YiW, AW and JX. Critical revision of the manuscript for important intellectual content: XZ and YiW. Statistical analysis: AW. Study supervision: YoW.

**Funding** Simcere Pharmaceutical Group supported the present study.

**Competing interests** None declared.

**Patient consent for publication** Parental/guardian consent obtained.

**Ethics approval** The study was approved by the institutional review board of each study centre and was conducted in accordance with the principles of the Declaration of Helsinki.

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

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

- Mendis S. Prevention and care of stroke in low- and middle-income countries; the need for a public health perspective. *Int J Stroke* 2010;5:86–91.
- Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743–800.
- Chamorro Á, Dirnagl U, Urra X, *et al*. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol* 2016;15:869–81.
- Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis* 2003;15:222–9.
- Wada T, Yasunaga H, Inokuchi R, *et al*. Effects of edaravone on early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. *J Neurol Sci* 2014;345:106–11.
- Wang Y, Liu M, Pu C. 2014 Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack. *Int J Stroke* 2017;12:302–20.
- Shinohara Y, Yanagihara T, Abe K, *et al*. II. Cerebral infarction/transient ischemic attack (TIA). *J Stroke Cerebrovasc Dis* 2011;20:S31–S73.
- Cheng B, Guo Y, Li C, *et al*. Edaravone protected PC12 cells against MPP(+)-cytotoxicity via inhibiting oxidative stress and up-regulating heme oxygenase-1 expression. *J Neurol Sci* 2014;343:115–9.
- 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 brain. *Stroke* 2005;36:2220–5.
- Wu HY, Tang Y, Gao LY, *et al*. The synergetic effect of edaravone and borneol in the rat model of ischemic stroke. *Eur J Pharmacol* 2014;740:522–31.
- Almeida JR, Souza GR, Silva JC, *et al*. Borneol, a bicyclic monoterpene alcohol, reduces nociceptive behavior and inflammatory response in mice. *ScientificWorldJournal* 2013;2013:1–5.
- Yoshida H, Yanai H, Namiki Y, *et al*. Neuroprotective effects of edaravone: a novel free radical scavenger in cerebrovascular injury. *CNS Drug Rev* 2006;12:9–20.
- Barinaga M. Finding new drugs to treat stroke. *Science* 1996;272:664–6.
- Schaller B, Graf R. Cerebral ischemia and reperfusion: the pathophysiologic concept as a basis for clinical therapy. *J Cereb Blood Flow Metab* 2004;24:351–71.
- Liu A, Fang H, Wei W, *et al*. Ischemic preconditioning protects against liver ischemia/reperfusion injury via heme oxygenase-1-mediated autophagy. *Crit Care Med* 2014;42:e762–e771.
- Abe K, Yuki S, Kogure K. Strong attenuation of ischemic and postischemic brain edema in rats by a novel free radical scavenger. *Stroke* 1988;19:480–5.

17. Nishi H, Watanabe T, Sakurai H, *et al.* Effect of MCI-186 on brain edema in rats. *Stroke* 1989;20:1236–40.
18. Mizuno A, Umemura K, Nakashima M. Inhibitory effect of MCI-186, a free radical scavenger, on cerebral ischemia following rat middle cerebral artery occlusion. *Gen Pharmacol* 1998;30:575–8.
19. Okabe TA, Kishimoto C, Shimada K, *et al.* Effects of MCI-186 (edaravone), a novel free radical scavenger, upon experimental atherosclerosis in apolipoprotein E-deficient mice. *Circ J* 2006;70:1216–9.
20. Houkin K, Nakayama N, Kamada K, *et al.* Neuroprotective effect of the free radical scavenger MCI-186 in patients with cerebral infarction: clinical evaluation using magnetic resonance imaging and spectroscopy. *J Stroke Cerebrovasc Dis* 1998;7:315–22.
21. Xu P, Li Y, Du SY, Sy D, *et al.* Comparative pharmacokinetics of borneol in cerebral ischemia-reperfusion and sham-operated rats. *J Zhejiang Univ Sci B* 2014;15:84–91.
22. Noor JI, Ueda Y, Ikeda T, *et al.* Edaravone inhibits lipid peroxidation in neonatal hypoxic-ischemic rats: an in vivo microdialysis study. *Neurosci Lett* 2007;414:5–9.
23. Cho KH, Oh JK, Jang YS, *et al.* Combination drug therapy using edaravone and Daio-Orengedoku-to after transient focal ischemia in rats. *Methods Find Exp Clin Pharmacol* 2008;30:443–50.
24. Nonaka Y, Shimazawa M, Yoshimura S, *et al.* Combination effects of normobaric hyperoxia and edaravone on focal cerebral ischemia-induced neuronal damage in mice. *Neurosci Lett* 2008;441:224–8.
25. Gao C, Li X, Li Y, *et al.* Pharmacokinetic interaction between puerarin and edaravone, and effect of borneol on the brain distribution kinetics of puerarin in rats. *J Pharm Pharmacol* 2010;62:360–7.
26. Pérez de la Ossa N, Dávalos A. Neuroprotection in cerebral infarction: the opportunity of new studies. *Cerebrovasc Dis* 2007;24 Suppl 1(Suppl 1):153–6.