SVN Stroke & Vascular Neurology

Safety and efficacy of GD-11 in patients with ischaemic stroke: a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial

Runhua Zhang ,[1,2] Gaifen Liu,[1,3] Xingquan Zhao ,[1] Yilong Wang ,[2,4] Zixiao Li ,[1,2] Guofang Chen,[5] Bo Liu,[6] Yun Ling,[7] Yongjun Wang ,[2,8] Shuya Li [2,8]

To cite: Zhang R, Liu G, Zhao X, *et al*. Safety and efficacy of GD-11 in patients with ischaemic stroke: a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. *Stroke & Vascular Neurology* 2024;**0**. doi:10.1136/svn-2024-003338

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/svn-2024-003338).

Received 18 April 2024
Accepted 25 July 2024

For numbered affiliations see end of article.

Correspondence to
Dr Shuya Li;
shuyali85@163.com

Dr Yongjun Wang;
yongjunwang@ncrcnd.org.cn

ABSTRACT

Background GD-11, a novel brain cytoprotective drug, was designed to be actively taken up and transported across the blood-brain barrier via the glucose transporter. This study aimed to evaluate the safety and efficacy of GD-11 for improving the recovery of patients with acute ischaemic stroke (AIS).

Methods A double-blind, randomised, placebo-controlled, phase 2 trial was conducted at 15 clinical sites in China. Patients aged 18–80 years with AIS within 48 hours were randomly assigned (1:1:1) to receive 160 mg GD-11, 80 mg GD-11 and placebo, two times a day for 10 days. The primary endpoint was a modified Rankin Scale (mRS) score of 0–1 at 90 days after treatment. The safety outcome was any adverse events within 90 days.

Results From 17 November 2022 to 22 March 2023, a total of 80 patients in the 160 mg GD-11 group, 79 patients in the 80 mg GD-11 group and 80 patients in the placebo group were included. The proportion of an mRS score of 0–1 at day 90 was 77.5% in the 160 mg GD-11 group, 72.2% in the 80 mg GD-11 group and 67.5% in the placebo group. Though no significant difference was found (p=0.3671), a numerically higher proportion was observed in the GD-11 group, especially in the 160 mg GD-11 group. The incidence of adverse events was similar across the three groups (p=0.1992).

Conclusion GD-11 was safe and well-tolerated. A dosage of GD-11 160 mg two times a day was recommended for a large trial to investigate the efficacy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The aim of the brain cytoprotective drug is to improve the preservation and recovery of the nervous system. However, most drugs failed to exert the cytoprotection in clinical.

WHAT THIS STUDY ADDS

⇒ GD-11, a novel brain cytoprotection designed to be actively taken up and transported across the blood-brain barrier via the nutrient transport channel-glucose transporter, was found to be safe and well-tolerated in patients with acute ischaemic stroke.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A dosage of GD-11 160 mg two times a day was recommended for a large trial to investigate the efficacy.

INTRODUCTION

Reperfusion including thrombolysis and endovascular thrombectomy is a potent strategy in the treatment of acute ischaemic stroke (AIS),[1] and significant advancements have been made in the past 20 years.[2] However, stroke is still the second leading cause of death globally and the third leading cause of disability-adjusted life years.[3] Considering the substantial burden of stroke and only a minority of patients with AIS eligible for reperfusion therapy due to strict time window constraints and contraindications,[4] the development of effective treatments remains a critical priority. Brain cytoprotective strategy which targets the ischaemic cascade has been advocated as an additional therapy.[4 5] While the achievement of cytoprotection aimed at tissue preservation and enhanced neurological function has been documented in preclinical models, the successful translation of these findings to clinical practice remains elusive.[6 7]

Edaravone, a free radical scavenger, has been shown neuroprotective effects by suppressing the free radicals, inhibiting endothelial cell injury and preventing neuronal death.[8–10] Despite being officially approved for the treatment of AIS in Japan in 2001 and being widely used in various Asian countries, including China and India,[1 11 12] the clinical efficacy of edaravone is constrained by its short circulation half-life and inadequate cerebral uptake.[13 14] Though edaravone can penetrate the blood-brain barrier (BBB) via lipid-mediated-free diffusion, the concentration of drugs reaching the brain is limited, resulting in attenuated therapeutic effect.

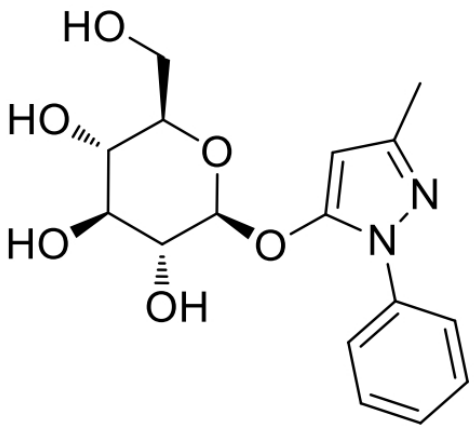

Figure 1 Chemical structure of GD-11.

There is an urgent need to increase the concentration of cytoprotective drugs in brain ischaemia to enhance the clinical efficacy. However, most drugs have a poor ability to penetrate BBB.[15] GD-11 (1-phenyl-3-methyl-5-O-D-gl ucoside (β)-pyrazole, figure 1) is an innovative cytoprotective agent designed to be proactively taken up and transported across the BBB to neuro cells via the nutrient transport channel-glucose transporter (GLUT). This unique mechanism of action can potentiate increased drug delivery to the brain, thereby enhancing neuroprotection. Experimental evidence suggests that GD-11 effectively accesses nerve cells through GLUT3, markedly escalating drug concentration within brain tissue in rodent models. Moreover, GD-11 demonstrates significant protective properties against neuronal damage mainly through the mechanisms of inhibition of neuronal apoptosis and injury via hypoxia-inducible factor-1α signalling pathway, and partial conversion into edaravone in plasma to effectively scavenge-free radicals and protect nerve cells. Following these observations, and based on the phase 1 study of GD-11 (unpublished), we designed the phase 2 study to assess the safety and efficacy of different doses of GD-11 for the treatment of patients with AIS within 48 hours.

METHODS

Study design

This study was a multicentre, double-blind, parallel-group, placebo-controlled, randomised, phase 2 trial investigating the safety and efficacy of intravenous administration of GD-11 in patients with AIS. Patients were recruited from 15 hospitals across China (online supplemental table 1).

Patients

Patients were eligible if they were 18–80 years of age and had an ischaemic stroke less than 48 hours before selection. Additional eligibility criteria were a National Institutes of Health Stroke Scale (NIHSS) score of 6–20, the sum score of upper and lower limbs ≥2 and no previous disability (modified Rankin Scale (mRS)≤1). All participants or their legally authorised delegates were required to provide signed and dated informed consent.

Exclusion criteria included any intracranial haemorrhage on brain image; severe disturbance of consciousness (score of consciousness in NIHSS>1); transient ischaemic attack; systolic blood pressure ≥220 mm Hg or diastolic blood pressure ≥120 mm Hg after treatment; severe mental disorders or dementia; active liver diseases; nephropathy or renal insufficiency; used neuroprotective drugs after stroke onset; having or planning to applicate interventional therapy; tumour and under antitumour treatment; terminally ill or expected survival time less than 90 days; pregnant or nursing, planning to become pregnant during the study; allergic to the substance in GD-11; history of operation within 4 weeks before enrolment and investigator evaluation affecting NIHSS or survival at 90 days; participation in another investigational study within 30 days before enrolment. A full list of inclusion and exclusion criteria is provided in online supplemental table 2.

Randomisation and masking

Patients were randomly assigned to receive 160 mg GD-11 two times a day, 80 mg GD-11 two times a day, or a placebo two times a day in a 1:1:1 ratio with a computer-generated allocation sequence. Treatment randomisation and allocation were centralised via an interactive web response system. Randomisation was stratified by treatment window (≤24 hours or >24 hours from stroke onset to treatment). GD-11 and placebo were provided in visually identical vials. Patients and all investigators were fully masked to treatment assignments.

Procedures

According to the pharmacokinetic/pharmacodynamic (PD/PK) studies in animals and GD-11 exposure in plasma, the GD-11 was administrated with a dosage of 80 mg or 160 mg two times a day for 10 days. The study drug was supplied in a vial containing 80 mg of lyophilised powder of GD-11. After selection, eligible patients were allocated to three groups: 160 mg GD-11 two times a day, 80 mg GD-11 two times a day, or placebo two times a day. The drug was dissolved with 100 mL saline and was administered via intravenous infusion in 30±10 min. The first drug was administered as soon as possible after randomisation. One dose drug was administered every 12 hours. A total of 20 doses of drugs were administered and the treatment lasted for 10 days.

Outcomes

The primary endpoint was an excellent outcome, defined as an mRS score of 0–1 on day 90. The secondary efficacy outcomes were the mRS score at day 90, evaluated by shift analysis; good outcome, defined as an mRS score of 0–2 at day 90; change of a total NIHSS score from baseline to day 10; the proportion of patients with a total NIHSS

score ≤1 or reduction of a total NIHSS score ≥4 from baseline to day 10; the proportion of a total NIHSS score ≤1 or reduction of a total NIHSS score ≥4 from baseline to day 30. The 30-day and 90-day mRS and NIHSS scores were evaluated by the trained investigator in person or by telephone.

The safety outcomes were the number and type of adverse events (AE) and all serious adverse events (SAE) that were related or not related to the study treatment. Patients had safety and efficacy assessments at visits scheduled on days 10, 30 and 90.

Statistical analysis

The primary analysis was done in the modified intention-to-treat (mITT) population, defined as all patients who received at least one dose of treatment and had at least one mRS score evaluated after enrolment. The binary outcome, including the primary efficacy endpoint (proportion of patients with an mRS of 0–1 at day 90), and secondary endpoints (good outcome defined by an mRS of 0–2; NIHSS score ≤1 or reduction of a total NIHSS score ≥4 from baseline to days 10 and 30) was analysed with a binary logistic regression model. The OR and corresponding 95% CI were reported. The secondary efficacy endpoint, multilevel mRS at day 90, was analysed by ordinal logistic regression. The ordinal shift analysis provides a common estimation of OR for improvement above considered cut points. The Kruskal-Wallis test was used to test the difference of changes in NIHSS scores from baseline to day 10 across the three groups. Missing data of efficacy outcome variables were imputed by the last observation carried forward approach. We also did a post hoc analysis to examine the treatment effect (primary outcome) in different subgroups. Additionally, we did a sensitivity analysis in the population with no imputed 90-day mRS score.

All safety analyses were done in the safety set, defined as all patients who received any amount of the study drug. We used a χ^2 or Fisher exact test to assess the difference in AEs in the three groups.

All tests were two-sided and p values below 0.05 were considered significant. All statistical analyses were done using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA).

Patient and public involvement

All participants were informed of the purpose and contents of the trial during recruitment, although they were not involved in setting the research question, the outcome measures, developing plans for the design or implementation of the study. Dissemination to the patients and members of the public will be through a press release and communication on publication of this study.

RESULTS

Baseline characteristics

Between 17 November 2022 and 22 March 2023, a total of 251 patients underwent screening, out of which 240 patients were randomly assigned to receive treatment. However, one patient in the placebo group did not receive the assigned treatment. Therefore, the mITT populations consisted of 239 patients, with 80 in the 160 mg GD-11 group, 79 in the 80 mg GD-11 group and 80 in the placebo group (figure 2). Among the mITT population, the mRS score at day 90 was available for 217 (91%) out of 239 patients, while the remaining 22 (9%) patients required imputation for the primary analysis. Patients included in the mITT had a median age of 65 years (IQR 58–71) and a median NIHSS score of 7 (IQR 6–8). The median time from stroke onset to treatment was 25 hours (IQR 18–34). A total of 191 (79.9%) had hypertension, 33 (13.8%) had diabetes, 78 (32.6%) had hyperlipidaemia and 79 (33.1%) had a history of previous stroke. In general, the baseline characteristics of the patients were similar in the three groups (table 1).

The safety set consisted of 80 patients in the 160 mg GD-11 group, 79 patients in the 80 mg GD-11 group and 80 patients in the placebo group. Among the treated patients, a total of 40 patients did not adhere to the study protocol (online supplemental table 3). Ultimately, the per-protocol analysis included 71 patients in the 160 mg GD-11 group, 63 patients in the 80 mg GD-11 group and 65 patients in the placebo group.

Safety analysis

In the safety population, 826 AEs were reported among 202 patients (online supplemental table 4). The incidences of AEs were similar in the three groups (63 (78.8%) for the 160 mg GD-11 group, 70 (88.6%) for the 80 mg GD-11 group, 69 (86.3%) for the placebo group, p=0.1992). Similarly, the mortality rates were comparable across the three groups (2 (2.5%) for the 160 mg GD-11 group, 3 (3.8%) for the 80 mg GD-11 group, 2 (2.5%) for the placebo group, p=0.8022) and all deaths were not attributed to the drug. SAE occurred in 9 (11.3%), 17 (21.5%) and 6 (7.5%) patients in the 160 mg GD-11 group, 80 mg GD-11 group and the placebo group, respectively. Table 2 depicts the common AEs occurring in 5% or more of patients in either treatment group. No significant difference in AEs was observed, except infectious pneumonia, urinary tract infection and vitamin B_{12} deficiency. The incidence of SAE differed significantly between the 80 mg GD-11 group and the placebo group (p=0.0077), but not significantly between the 160 mg GD-11 group and the placebo group (p=0.5889). Details of SAE were listed in online supplemental table 5.

Efficacy outcomes

The primary endpoint of mRS score 0–1 at day 90 was achieved by 62 (77.5%) of 80 patients in the 160 mg GD-11 group, 57 (72.2%) of 79 patients in the 80 mg GD-11 group and 54 (67.5%) of 80 patients in the placebo group (p=0.3671, figure 3). The difference in the primary endpoint between each of the two GD-11 groups and the placebo group was not statistically significant (OR=1.66 (95% CI 0.82 to 3.37) for the 160 mg GD-11 group

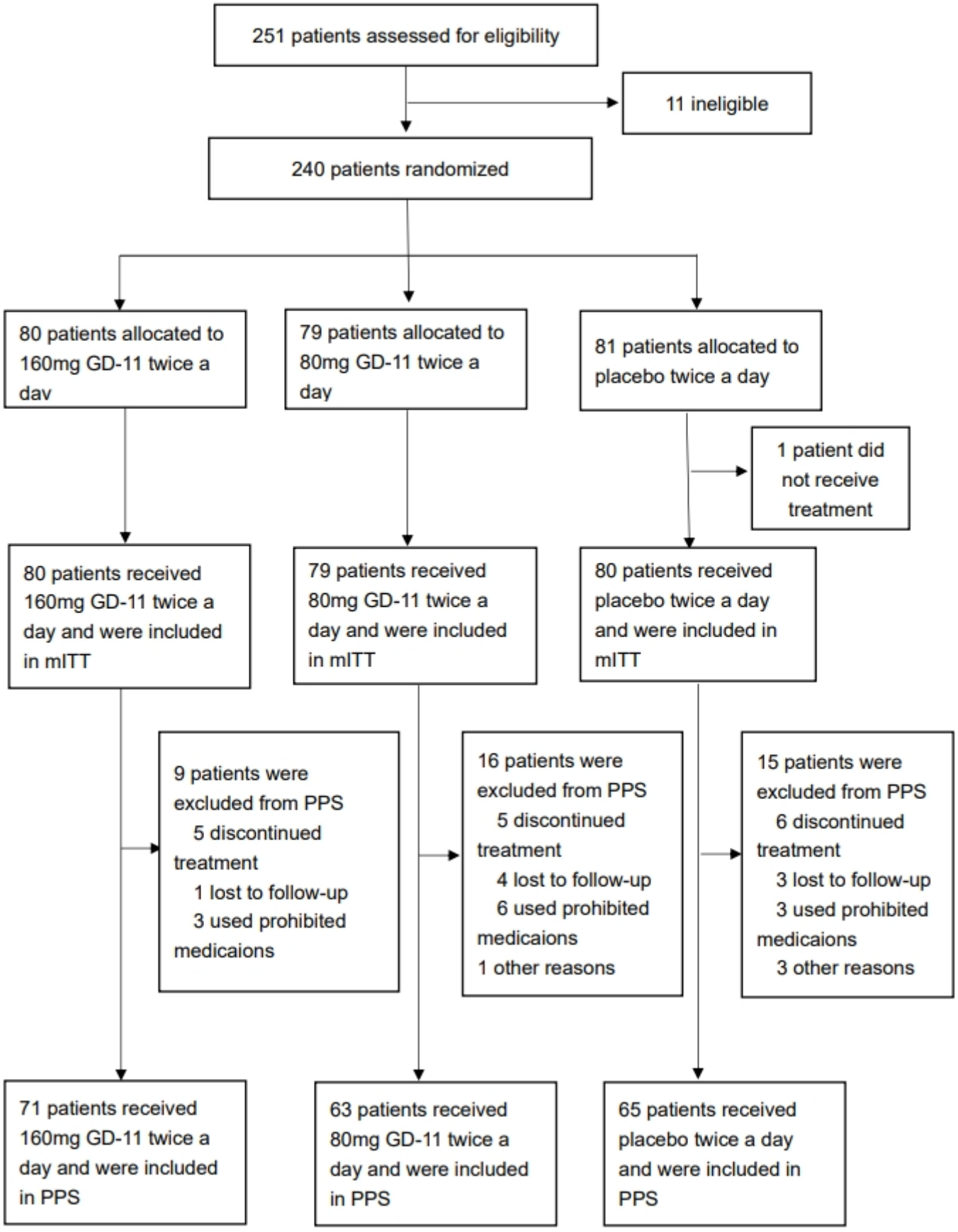

Figure 2 Trial profile. mITT, modified intention-to-treat; PPS, per-protocol set.

Table 1 Baseline characteristics in the modified intention-to-treat population

	GD-11 160 mg (n=80)	GD-11 80 mg (n=79)	Placebo (n=80)	P value
Age (years)				
Median (IQR)	64 (58.5–71)	65(58–70)	65(58–72)	0.7552
<65	41 (51.3%)	39 (49.4%)	36 (45.0%)	0.7196
≥65	39 (48.8%)	40 (50.6%)	44 (55.0%)	
Sex				
Female	62 (77.5%)	57 (72.2%)	56 (70.0%)	0.5443
Male	18 (22.5%)	22 (27.8%)	24 (30.0%)	
NIHSS score				
Median (IQR)	7 (6–8)	7 (6–8)	7 (6–8)	0.7005
Previous mRS				
0	73 (91.3%)	69 (87.3%)	76 (95.0%)	0.2335
1	7 (8.8%)	10 (12.7%)	4 (5.0%)	
Weight (kg)				
Median (IQR)	68.25 (62–75)	65 (60–72.5)	68 (60–75)	0.4271
Systolic pressure (mm Hg)				
Mean (SD)	142.06±16.76	147.78±20.53	144.75±16.61	0.1376
Diastolic pressure (mm Hg)				
Mean (SD)	84.59±10.41	87.66±12.68	84.95±10.99	0.1810
Smoking status				
Past	6 (7.5%)	5 (6.3%)	8 (10.0%)	0.3648
No	47 (58.8%)	54 (68.4%)	42 (52.5%)	
Current	27 (33.8%)	20 (25.3%)	30 (37.5%)	
Hypertension	62 (77.5%)	66 (83.5%)	63 (78.8%)	0.6045
Diabetes	11 (13.8%)	10 (12.7%)	12 (15.0%)	0.9123
Hyperlipidaemia	28 (35.0%)	23 (29.1%)	27 (33.8%)	0.7067
Previous stroke history				
Yes	27 (33.8%)	26 (32.9%)	26 (32.5%)	0.9854
No	53 (66.3%)	53 (67.1%)	54 (67.5%)	
rtPA	8 (10.0%)	7 (8.86%)	8 (10.0%)	0.9613
TOAST				
LAA	49 (61.3%)	47 (59.5%)	48 (60.0%)	0.5174
CE	4 (5.0%)	6 (7.6%)	2 (2.5%)	
SAO	22 (27.5%)	25 (31.6%)	25 (31.3%)	
Other	5 (6.3%)	1 (1.3%)	5 (6.3%)	
Time of treatment from onset (hours)				
Median (IQR)	28.0 (20–35.6)	24.0 (18–33.6)	24.8 (17.7–33.4)	0.8176
<24	39 (48.8%)	40 (50.6%)	40 (50.0%)	0.9712
≥24	41 (51.3%)	39 (49.4%)	40 (50.0%)	

CE, cardiogenic embolism; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; SAO, small artery occlusion; TOAST, Trail of ORG10172 in Acute Stroke Treatment.

compared with the placebo group and OR=1.26 (95% CI 1.26 to 2.49) for the 80 mg GD-11 group compared with the placebo group) (table 3). However, there was a possible higher trend in the proportion of mRS score 0–1 in the 160 mg and the 80 mg GD-11 groups compared with the placebo group (77.5% and 72.2% vs 67.5%). The secondary endpoints did not reveal any significant differences among the three groups (table 3). The results were similar in the per-protocol populations (online supplemental figure and table 6). No significant difference in the primary endpoint was observed in any subgroups (online supplemental table 7). The result for the primary

Table 2 Summary of adverse events occurring in 5% or more of patients in either group

	GD-11 160 mg (n=80)	GD-11 80 mg (n=79)	Placebo (n=80)	P value
Constipation	13 (16.3%)	18 (22.8%)	13 (16.3%)	0.4937
Cerebral infarction	4 (5.0%)	7 (8.9%)	2 (2.5%)	0.1860
Hypoproteinaemia	7 (8.8%)	7 (8.9%)	6 (7.5%)	0.9582
Hypokalaemia	10 (12.5%)	6 (7.6%)	9 (11.3%)	0.6450
Fever	2 (2.5%)	7 (8.9%)	4 (5.0%)	0.1860
Abdominal discomfort	1 (1.3%)	3 (3.8%)	4 (5.0%)	0.4535
Diarrhoea	0 (0.0%)	4 (5.1%)	4 (5.0%)	0.1230
Abnormal liver function	8 (10.0%)	10 (12.7%)	8 (10.0%)	0.8402
Infectious pneumonia	1 (1.3%)	5 (6.3%)	0 (0.0%)	0.0185
Hyperuricaemia	3 (3.8%)	6 (7.6%)	4 (5.0%)	0.5245
Hyperhomocysteinaemia	10 (12.5%)	4 (5.1%)	11 (13.8%)	0.1577
Hyperlipidaemia	4 (5.0%)	6 (7.6%)	7 (8.8%)	0.6699
Anxiety	3 (3.8%)	6 (7.6%)	4 (5.0%)	0.5245
Progressive apoplexy	2 (2.5%)	4 (5.1%)	1 (1.3%)	0.3161
Carotid arteriosclerosis	1 (1.3%)	2 (2.5%)	4 (5.0%)	0.4125
Cough	3 (3.8%)	4 (5.1%)	4 (5.0%)	0.9314
Urinary tract infection	4 (5.0%)	3 (3.8%)	15 (18.8%)	0.0026
Anaemia	2 (2.5%)	6 (7.6%)	2 (2.5%)	0.1865
Upper respiratory tract infection	7 (8.8%)	6 (7.6%)	3 (3.8%)	0.4715
Renal impairment	2 (2.5%)	4 (5.1%)	3 (3.8%)	0.6470
Insomnia	8 (10.0%)	9 (11.4%)	5 (6.3%)	0.5262
Anorexia	0 (0.0%)	1 (1.3%)	4 (5.0%)	0.0900
Sleep disorder	3 (3.8%)	2 (2.5%)	4 (5.0%)	0.9113
Poor sleep quality	2 (2.5%)	4 (5.1%)	4 (5.0%)	0.7227
Giddy	5 (6.3%)	4 (5.1%)	4 (5.0%)	1.0000
Vitamin B_{12} deficiency	0 (0.0%)	5 (6.3%)	2 (2.5%)	0.0361
Toothache	1 (1.3%)	0 (0.0%)	4 (5.0%)	0.1306

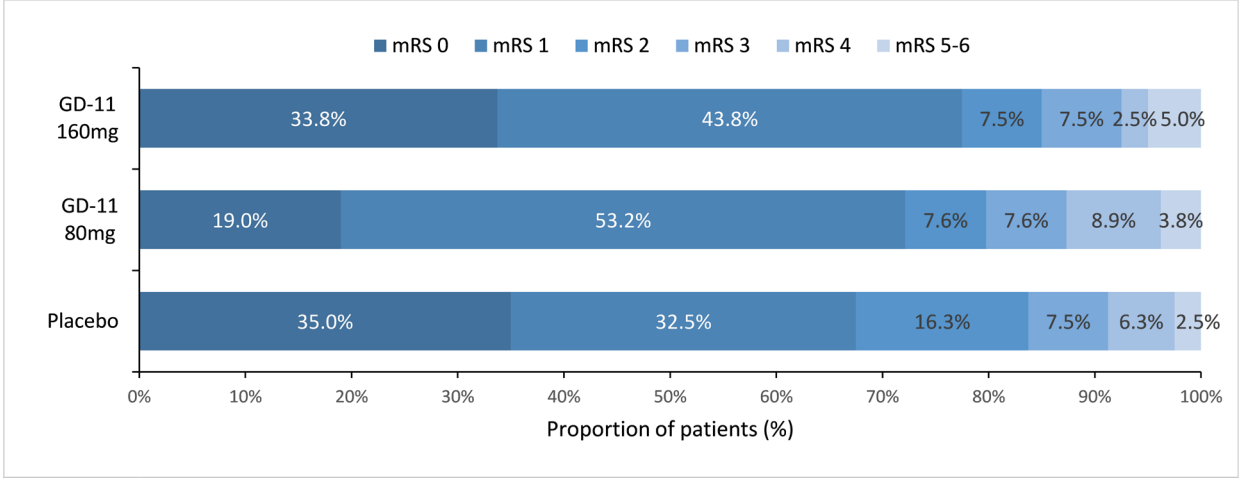

Figure 3 Modified Rankin Scale score at day 90 in the modified intention-to-treat population. mRS, modified Rankin Scale.

Table 3 Primary and secondary efficacy outcomes

Outcome	GD-11 160 mg (n=80)	GD-11 80 mg (n=79)	Placebo (n=80)
Primary outcome			
mRS≤1			
n (%)	62 (77.5)	57 (72.2)	54 (67.5)
OR (95% CI)	1.66 (0.82 to 3.35)	1.25 (0.63 to 2.46)	Ref
P value	0.22	0.92	
Secondary outcomes			
mRS as ordinal shift			
Common OR	1.17 (0.66–2.07)	0.71 (0.40–1.26)	Ref
P value	0.19	0.10	
mRS≤2			
n (%)	68 (85.0)	63 (79.7)	67 (83.8)
OR (95% CI)	1.1 (0.47 to 2.58)	0.76 (0.34 to 1.71)	Ref
P value	0.54	0.37	
NIHSS score changes between baseline and day 10			
Median (IQR)	−3 (−5 to −2)	−3 (−5 to −2)	−3 (−4 to −2)
Mean (SD)	−2.98 (0.35)	−3.06 (0.29)	−2.79 (0.26)
P value	0.27	0.40	
NIHSS score ≤1 or reduction ≥4 from baseline to day 10			
n (%)	34 (42.5)	38 (48.1)	33 (41.3)
OR (95% CI)	1.05 (0.56 to 1.97)	1.32 (0.71 to 2.47)	Ref
P value	0.75	0.36	
NIHSS score ≤1 or reduction ≥4 from baseline to day 30			
n (%)	57 (71.3)	59 (74.7)	59 (73.8)
OR (95% CI)	0.88 (0.44 to 1.77)	1.05 (0.52 to 2.14)	Ref
P value	0.62	0.72	

mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

endpoint was similar in the population with no imputed 90-day mRS score (online supplemental table 8).

DISCUSSION

This multicentre, randomisation, double-blind, placebo-controlled, phase 2 trial demonstrated that administration of GD-11 at a dose of 80 mg or 160 mg two times a day was safe and tolerated in patients with ischaemic stroke. There was a higher trend but no significant difference in the proportion of mRS 0–1 for both GD-11 groups compared with the placebo group.

The ischaemic-initiated stroke cascade, characterised by excitotoxicity, oxidative and nitrosative stress and inflammation, is the primary target for brain cytoprotective agents.[2 16 17] Regardless of the specific mechanism of the cytoprotective drug targeted, the drug must reach to the ischaemic brain tissue or cerebral endothelium.[5] Owing to the BBB, only lipophilic small molecules are capable of crossing the brain endothelium.[18 19] During ischaemia, the BBB becomes hyperpermeable due to disruption of adherens junctions.[20 21] However, the BBB within the penumbra may be not destroyed completely and yet preserve its impermeable characteristics to some extent. Only relying on the method of simple diffusion, the concentration of drug reached the neuro cells is limited. GD-11 is an innovative targeted neuroprotectant specifically designed and developed to target GLUT3, a highly expressed protein responsible for the transportation of glucose molecules in the neuros.[22–25] In the PD/PK study, after intravenous infusion of GD-11 12 mg/kg, the concentration of GD-11 in the rat brain was higher than that of edaravone and the brain tissue exposure area under curve (AUC) of GD-11 was 16.3 times than that of edaravone. GD-11 may exert pharmacodynamic effects through both the native form and the metabolic derivative of edaravone.

In this trial, though there was no significant difference in the total incidence of AE, we found the incidences of infectious pneumonia, urinary tract infection and vitamin B_{12} deficiency were significantly different across the three groups. The number of patients with infectious pneumonia in the GD-11 160 mg group, GD-11 80 mg

group and the placebo group were 1, 5 and 0, respectively. Although the incidence of infectious pneumonia was higher in the GD-11 80 mg group compared with the placebo group, the investigator concluded that all cases of infectious pneumonia in the GD-11 80 mg group were not related to the trial drug. The only case of infectious pneumonia in the GD-160 mg group was possible related with the trial drug. The number of vitamin B_{12} deficiencies in the GD-11 160 mg group, GD-11 80 mg group and the placebo group were 0, 5 and 2, respectively. Among the seven AEs of vitamin B_{12} deficiency, only one in the GD-11 80 mg group was possibly related to the trial drug. Additionally, we found the incidence of urinary tract infection in both GD-11 groups was lower than that in the placebo group. All AEs of urinary tract infection were not related to the trial drug. A dose-dependent correlation was not observed between medication dosage and the incidence of AEs. Among the 38 SAEs reported in 32 patients, 3 SAEs (severe pneumonia, type I respiratory failure and heart failure) occurred in a single patient in the 160 mg GD-11 group and these were likely associated with the study medication. Post-therapeutic recovery from type I respiratory failure and heart failure was achieved without residual effects; however, the recovery from pneumonia was enduring with residual impacts. The underlying mechanism of these AEs remains obscure. Due to the small sample size, this result should be considered exploratory. In future studies, the association of pneumonia, respiratory failure and heart failure should be further investigated.

Although this trial revealed no statistically significant difference in the primary and secondary endpoints compared with the control group, a numerically high number of patients with mRS 0–1 was observed at day 90 in both GD-11 groups. We found differences of 10% and 4.7% in the proportion of mRS 0–1 between the GD-11 160 mg group, the GD-11 80 mg group and the control group. In terms of the primary outcome, the efficacy was more pronounced in the GD-11 160 mg group than in the GD-11 80 mg group. In light of the safety and efficacy results, it is recommended to proceed with a phase 3 clinical trial that administers a dosage of 160 mg GD-11 two times a day.

This study has some limitations. First, the sample size of this phase 2 study was relatively small, which may have limited the statistical power to detect the efficacy in some subgroups of interest, such as in patients with thrombolysis. Larger scale studies are needed to confirm the efficacy of GD-11 in the treatment of AIS. Second, the study was limited to a specific patient population with moderate severity of stroke (NIHSS score of 6–20) and excluded those with severe disturbance of consciousness, which limited the population extrapolation. The safety and efficacy of GD-11 in patients with more severe or less severe strokes remain to be investigated. Third, the effect of GD-11 and edaravone was not compared. Since there is abundant clinical data on edaravone and edaravone is one of the metabolites, we may use edaravone as a compared drug. However, considering the objective of this trial was to evaluate the safety and efficacy of GD-11 and edaravone was not a standard treatment in current clinical practice, the placebo used as the control group was more reasonable. Fourth, the degree of perfusion was not recorded, which may provide information on the direct effect of the trial drug.

CONCLUSION

Administration of GD-11 at a dosage of 160 mg two times a day was safe and well-tolerated in patients with AIS. A large trial is essential to ascertain the efficacy of GD-11.

Author affiliations
[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]China National Clinical Research Center for Neurological Diseases, Beijing, China
[3]Department of Neurology, Beijing Tiantan Hospital, Beijing, China
[4]Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[5]Xuzhou Central Hospital, Xuzhou, Jiangsu, China
[6]Inner Mongolia University of Science and Technology, Baotou, Inner Mongolia, China
[7]Nanshi Hospital of Nangyang, Nanyang, Henan, China
[8]Department of Neurology and Department of Clinical Trial Center, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

X Yilong Wang @yilong

Contributors SL contributed to study design. RZ wrote the first draft of the manuscript. RZ, GL, SL and YW contributed to data interpretation, reviewed the manuscript and revisions. GC, BL and YL contributed to patient supplying. XZ, ZL and YW contributed to critical revision of the manuscript for important intellectual content. SL is the guarantor of this manuscript.

Funding This work was supported by Beijing Municipal Science & Technology Commission (Z221100007422050) and Capital's Funds for Health Improvement and Research (2020-1-2041, 2022-2G-2049).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by IRB of Beijing Tiantan Hospital, Capital Medical University (YW2022-039-02). 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 upon reasonable request. The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ORCID iDs
Runhua Zhang http://orcid.org/0000-0003-4825-191X
Xingquan Zhao http://orcid.org/0000-0001-8345-5147
Yilong Wang http://orcid.org/0000-0002-3267-0039
Zixiao Li http://orcid.org/0000-0002-4713-5418

Yongjun Wang http://orcid.org/0000-0002-9976-2341
Shuya Li http://orcid.org/0000-0002-7263-0365

REFERENCES

1 Xu J, Wang A, Meng X, *et al*. Edaravone dexborneol versus edaravone alone for the treatment of acute ischemic stroke. *Stroke* 2021;52:772–80.
2 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.
3 Feigin VL, Stark BA, Johnson CO, *et al*. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol* 2021;20:795–820.
4 Haupt M, Gerner ST, Bähr M, *et al*. Quest for quality in translational stroke research-a new dawn for neuroprotection? *Int J Mol Sci* 2022;23:5381.
5 Fisher M, Savitz SI. Pharmacological brain cytoprotection in acute ischaemic stroke - renewed hope in the reperfusion era. *Nat Rev Neurol* 2022;18:193–202.
6 Haupt M, Gerner ST, Bähr M, *et al*. Neuroprotective strategies for ischemic stroke-future perspectives. *Int J Mol Sci* 2023;24:4334.
7 Chamorro Á, Lo EH, Renú A, *et al*. The future of neuroprotection in stroke. *J Neurol Neurosurg Psychiatry* 2021;92:129–35.
8 Watanabe T, Morita I, Nishi H, *et al*. Preventive effect of MCI-186 on 15-HPETE induced vascular endothelial cell injury in vitro. *Prostaglandins Leukot Essent Fatty Acids* 1988;33:81–7.
9 Ren Y, Wei B, Song X, *et al*. Edaravone's free radical scavenging mechanisms of neuroprotection against cerebral ischemia: review of the literature. *Int J Neurosci* 2015;125:555–65.
10 Lapchak PA. A critical assessment of edaravone acute ischemic stroke efficacy trials: is edaravone an effective neuroprotective therapy? *Expert Opin Pharmacother* 2010;11:1753–63.
11 Fidalgo M, Ricardo Pires J, Viseu I, *et al*. Edaravone for acute ischemic stroke - Systematic review with meta-analysis. *Clin Neurol Neurosurg* 2022;219:107299.
12 Sharma P, Sinha M, Shukla R, *et al*. A randomized controlled clinical trial to compare the safety and efficacy of edaravone in acute ischemic stroke. *Ann Indian Acad Neurol* 2011;14:103–6.
13 Kobayashi S, Fukuma S, Ikenoue T, *et al*. Effect of edaravone on neurological symptoms in real-world patients with acute ischemic stroke. *Stroke* 2019;50:1805–11.
14 Jin Q, Cai Y, Li S, *et al*. Edaravone-encapsulated agonistic micelles rescue ischemic brain tissue by tuning blood-brain barrier permeability. *Theranostics* 2017;7:884–98.
15 Xu X, Chen M, Zhu D. Reperfusion and cytoprotective agents are a mutually beneficial pair in ischaemic stroke therapy: an overview of pathophysiology, pharmacological targets and candidate drugs focusing on excitotoxicity and free radical. *Stroke Vasc Neurol* 2023.
16 Lo EH, Moskowitz MA, Jacobs TP. Exciting, radical, suicidal. *Stroke* 2005;36:189–92.
17 Wiendl H, Elger C, Förstl H, *et al*. Gaps between aims and achievements in therapeutic modification of neuronal damage ("Neuroprotection"). *Neurotherapeutics* 2015;12:449–54.
18 Dong X. Current strategies for brain drug delivery. *Theranostics* 2018;8:1481–93.
19 Pardridge WM. Drug transport across the blood–brain barrier. *J Cereb Blood Flow Metab* 2012;32:1959–72.
20 Gao X, Kouklis P, Xu N, *et al*. Reversibility of increased microvessel permeability in response to VE-cadherin disassembly. *Am J Physiol Lung Cell Mol Physiol* 2000;279:L1218–25.
21 Shiraishi K, Wang Z, Kokuryo D, *et al*. A polymeric micelle magnetic resonance imaging (MRI) contrast agent reveals blood-brain barrier (BBB) permeability for macromolecules in cerebral ischemia-reperfusion injury. *J Control Release* 2017;253:165–71.
22 Maher F, Davies-Hill TM, Simpson IA. Substrate specificity and kinetic parameters of GLUT3 in rat cerebellar granule neurons. *Biochem J* 1996;315:827–31.
23 Gerhart DZ, Broderius MA, Borson ND, *et al*. Neurons and microvessels express the brain glucose transporter protein GLUT3. *Proc Natl Acad Sci USA* 1992;89:733–7.
24 Simpson IA, Carruthers A, Vannucci SJ. Supply and demand in cerebral energy metabolism: the role of nutrient transporters. *J Cereb Blood Flow Metab* 2007;27:1766–91.
25 Patching SG. Glucose transporters at the blood-brain barrier: function, regulation and gateways for drug delivery. *Mol Neurobiol* 2017;54:1046–77.