Safety and efficacy of GD-11 in patients with ischemic stroke: a multicenter, double-blind, randomized, placebo-controlled, phase 2 trial

Supplementary materials

Table 1. Participating sites and the number of patients enrolled in each site

	Sites	N
1	Cangzhou Central Hospital	12
2	Daqing People's Hospital	13
3	Daqing Oilfield General Hospital	4
4	Hainan Provincial People's Hospital	8
5	Liuzhou Workers Hospital	7
6	Nanshi Hospital of Nanyang	31
7	The First Affiliated Hospital of Nanyang Medical College	18
8	The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology	42
9	Pingxiang People's Hospital	24
10	Shanghai Pudong New Area People's Hospital	10
11	Taizhou First People's Hospital	9
12	Yijishan Hospital, Wannan Medical College	5
13	Wuhan Fourth Hospital	10
14	Xuzhou Central Hospital	33
15	Xuzhou Central Hospital (Xincheng Branch)	13

Table 2. Inclusion and exclusion criteria

Inclusion criteria
1. Age ≥ 18 years and < 81 years, gender is not limited;
2. National Institutes of Health Stroke Scale (NIHSS) score after this attack: 6 ⩽ NIHSS ⩽ 20 points, and the sum of scores for item 5 (upper limb) and item 6 (lower limb) ⩾ 2 points;
3. Onset within 48 hours (including 48 hours);
4. Diagnosed with ischemic stroke according to the "2019 Diagnostic Criteria for Various Major Cerebrovascular Diseases in China," for either first-time stroke patients or those who have recovered well from their last stroke (mRS score ⩽ 1 before this attack);
5. Obtain informed consent signed voluntarily by the patient or their legal representative, which has been approved by the Ethics Committee.
Exclusion criteria
1. Intracranial hemorrhagic diseases seen on cranial imaging: hemorrhagic stroke, extradural hematoma, intracranial hematoma, ventricular hemorrhage, subarachnoid hemorrhage, etc.; if it is only a trace of bleeding, the researcher can judge whether it is suitable for inclusion;
2. Severe consciousness disturbance: score for NIHSS item 1a (consciousness level) > 1 point;
3. Transient ischemic attack (TIA);
4. Patient's blood pressure remains ≥ 220 mmHg for systolic and ≥120 mmHg for diastolic after control;
5. Patients with a history of severe mental disorders and dementia;
6. Diagnosed with severe active liver disease, such as acute hepatitis, chronic active hepatitis, cirrhosis, etc.; or ALT or AST > 2.0 × ULN;
7. Diagnosed with severe active kidney disease, renal insufficiency; or serum creatinine > 1.5 × ULN;
8. After the onset of this disease, neuroprotective drugs have been used in the marketing, such as Edaravone, Edara Dexborneol, Nimodipine, Ganglioside, Citicoline, Piracetam, Oxiracetam, Butylphthalide, Human Urinary Kallidinogenase, Cinepazide, Mouse Nerve Growth Factor, Cerebroprotein Hydrolysate, Deproteinized Calf Blood Injection, Deproteinized Hemoderivative of calf blood, etc.;
9. Have used or plan to use thrombectomy or interventional treatment after this attack;
10. Have a history of diagnosed concurrent malignant tumors and are undergoing anti-tumor treatment;
11. Have a history of diagnosed with severe systemic diseases, with a predicted survival period of < 90 days;
12. Patients who are pregnant, lactating, or have a pregnancy potential and plan to become pregnant during the trial period;
13. Patients with a known history of allergy to the components of GD-11 for injection;
14. Have a history of major surgery within 4 weeks before enrollment and the researcher assess that it affects the neurofunction score or the survival period of 90 days.

15. Have participated in another clinical study within 30 days prior to randomization or are currently participating in another clinical study;
16. The investigator considers the patient unsuitable for participation in this clinical study.

Table 3. Protocol deviations in the modified intention-to-treat population

	GD-11 160mg (n=80)	GD-11 80mg (n=79)	Placebo (n=80)
At least one protocol deviation	6 (7.5%)	8 (10.1%)	7 (8.8%)
Concomitant medication	3 (3.8%)	8 (10.1%)	3 (3.8%)
Dosage violation	1 (1.3%)	1 (1.3%)	0 (0%)
Randomization and blinding	1 (1.3%)	0 (0%)	1 (1.3%)
SAE Report	1 (1.3%)	0 (0%)	0 (0%)
Visit window deviation	1 (1.3%)	0 (0%)	3 (3.8%)

Table 4. Adverse events by MedDRA system organ class

	GD-11 160mg (n=80)	GD-11 80mg (n=79)	Placebo (n=80)	p
Blood and lymphatic system	3 (3.8%)	7 (8.9%)	3 (3.8%)	0.2704
Cardiac disorders	8 (10.0%)	10 (12.7%)	10 (12.5%)	0.8424
Congenital，familial and genetic disorders	1 (1.3%)	0 (0.0%)	1 (1.3%)	1.0000
Ear and labyrinth disorders	0 (0.0%)	2 (2.5%)	1 (1.3%)	0.3277
Endocrine disorders	1 (1.3%)	0 (0.0%)	1 (1.3%)	1.0000
Eye disorders	1 (1.3%)	1 (1.3%)	0 (0.0%)	0.7750
Gastrointestinal disorders	18 (22.5%)	31 (39.2%)	26 (32.5%)	0.0727
General disorders and administration site condition	6 (7.5%)	14 (17.7%)	8 (10.0%)	0.1132
Hepatobiliary disorders	8 (10.0%)	11 (13.9%)	9 (11.3%)	0.7346
Immune system disorders	2 (2.5%)	1 (1.3%)	0 (0.0%)	0.5499
Infections and infestation	21 (26.3%)	19 (24.1%)	23 (28.8%)	0.7973
Injury，poisoning and procedural complications	2 (2.5%)	4 (5.1%)	1 (1.3%)	0.3161
Investigations	17 (21.3%)	17 (21.5%)	20 (25.0%)	0.8189
Metabolism and nutrition disorders	33 (41.3%)	35 (44.3%)	35 (43.8%)	0.9175
Musculoskeletal and connective tissue disorders	5 (6.3%)	5 (6.3%)	7 (8.8%)	0.7834
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0.7750
Nervous system disorders	16 (20.0%)	22 (27.8%)	19 (23.8%)	0.5095
Psychiatric disorders	17 (21.3%)	24 (30.4%)	18 (22.5%)	0.3515
Renal and urinary disorders	8 (10.0%)	10 (12.7%)	7 (8.8%)	0.7134
Reproductive system and breast disorders	0 (0.0%)	4 (5.1%)	2 (2.5%)	0.0890
Respiratory, thoracic and mediastinal disorders	10 (12.5%)	8 (10.1%)	9 (11.3%)	0.8942
Skin and subcutaneous tissue disorders	2 (2.5%)	5 (6.3%)	2 (2.5%)	0.4397
Vascular disorders	6 (7.5%)	2 (2.5%)	2 (2.5%)	0.3116

Table 5. The number of serious adverse events in the safety population

	GD-11 160mg (n=80)	GD-11 80mg (n=79)	Placebo (n=80)
Elevated white blood cell count	0	1	0
Cerebral infarction	2	6	2
Postherpetic neuralgia	1	0	0
Fever	1	0	0
Pulmonary inflammation	1	0	1
Pulmonary embolism	1	0	0
Abnormal liver function	0	1	0
Infectious pneumonia	1	1	0
Respiratory failure	1	0	0
Acute myocardial infarction	0	2	0
Progressive apoplexy	0	1	0
Carotid artery occlusion	0	0	1
Chronic osteomyelitis	0	1	0
Urinary tract infection	0	0	1
Radiculopathy	0	1	0
Dizziness	0	1	0
Peripheral arterial occlusive disease	1	0	0
Pericardial effusion	0	1	0
Heart failure	1	0	0
Cardiac respiratory arrest	1	0	1
Thrombotic cerebral infarction	1	0	0
Subdural hematoma	0	1	0
Herniated disc	0	1	0
Sudden death	0	1	1

Table 6. Primary and secondary efficacy outcomes in per-protocol population

Outcome	GD-11 160mg (n=71)	GD-11 80mg (n=63)	Placebo (n=65)
Primary outcome			
mRS≤1			
n (%)	58 (81.7%)	49 (77.8%)	49 (75.4%)
OR (95% CI)	1.46 (0.64-3.32)	1.14 (0.5-2.59)	Ref
p value	0.4	0.88	
Secondary outcomes			
mRS as ordinal shift			
Common OR	1.07 (0.57-2.01)	0.67 (0.35-1.28)	Ref
p value	0.33	0.12	
mRS≤2			
n (%)	64 (90.1%)	53 (84.1%)	59 (90.8%)
OR (95% CI)	0.93 (0.3-2.93)	0.54 (0.18-1.58)	Ref
p value	0.63	0.20	
NIHSS score changes between baseline and day 10			
Median (IQR)	-3 (-5 to -2)	-3 (-5 to -2)	-3 (-5 to -2)
Mean (SD)	-3.48 (0.29)	-3.30 (0.30)	-3.12 (0.26)
p value	0.24	0.57	
NIHSS score≤1 or reduction ≥4 from baseline to day 10			
n (%)	32 (45.1%)	30 (47.6%)	30 (46.2%)
OR (95% CI)	0.96 (0.49-1.88)	1.06 (0.53-2.12)	Ref
p value	0.81	0.79	
NIHSS score≤1 or reduction ≥4 from baseline to day 30			
n (%)	54 (76.1%)	49 (77.8%)	53 (81.5%)
OR (95% CI)	0.72 (0.31-1.65)	0.79 (0.33-1.88)	Ref
p value	0.55	0.85	

Table 7. Subgroup analysis of primary endpoints

Subgroups		GD-11 160mg	GD-11 80mg	Placebo
Males	OR (95% CI)	2.26 (1.00-5.12)	1.84 (0.82-4.14)	Ref
	p value	0.17	0.58	
Females	OR (95% CI)	0.68 (0.16-2.85)	0.46 (0.12-1.71)	Ref
	p value	0.99	0.31	
Age <65	OR (95% CI)	1.56 (0.56-4.36)	0.88 (0.33-2.33)	Ref
	p value	0.26	0.41	
Age ≥65	OR (95% CI)	1.72 (0.65-4.55)	1.78 (0.68-4.7)	Ref
	p value	0.57	0.50	
BMI<24	OR (95% CI)	2.14 (0.72-6.37)	1.27 (0.51-3.15)	Ref
	p value	0.19	0.73	
BMI≥24	OR (95% CI)	1.24 (0.48-3.19)	1.62 (0.53-4.9)	Ref
	p value	0.95	0.46	
NIHSS<7	OR (95% CI)	0.6 (0.13-2.77)	0.72 (0.16-3.28)	Ref
	p value	0.58	0.90	
NIHSS≥7	OR (95% CI)	2.27 (0.98-5.27)	1.26 (0.55-2.86)	Ref
	p value	0.07	0.63	

Table 8. Primary efficacy outcomes in patients with no missing 90-day mRS score

Outcome	GD-11 160mg (n=74)	GD-11 80mg (n= 71)	Placebo (n=72)
mRS≤1			
n (%)	60 (81.08%)	54 (76.06%)	52 (72.22%)
OR (95% CI)	1.65 (0.76-3.59)	1.22 (0.58-2.59)	Ref
p value	0.26	0.88	

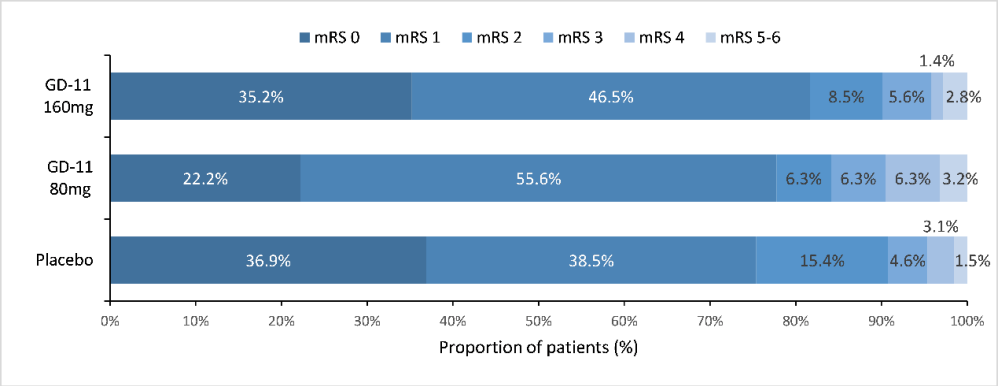

Figure. Modified Rankin Scale score at day 90 in the per-protocol set