Supplemental Table 1. **Participation centres**

No.	Hospital	Primary Investigators
1	Tianjin Huanhu Hospital	Jialing Wu
2	Jiyuan Chinese Medical Hospital	Hongqin Yang
3	Sui Chinese Medical Hospital	Ying Li
4	The Third People's Hospital of Liaocheng	Liguo Chang
5	China-Japan Union Hospital of Jilin University	Ying Xing
6	Weihai Wendeng District People's Hospital	Jinguo Zhao
7	Ningjin People's Hospital	Chunjie Yang
8	Nanle Zhongxing Hospital	Yanna Ma
9	Xingyang People's Hospital	Haijun Wang
10	Tianjin Xiqing Hospital	Liqing Dong
11	North China University of Science and Technology Affiliated Hospital	Bin Liu
12	Beijing Tiantan Hospital, Capital Medical University	Yilong Wang
13	Biyang People's Hospital	Shuo Zhang
14	First Hospital of Shanxi Medical University	Shaoshuai Wang
15	Yuci District People's Hospital	Aishe Zhao
16	Chongqing University Three Gorges Hospital	Shengli Chen
17	Mengzhou People's Hospital	Dali Li
18	Luoyang Central Hospital	Zhihui Duan
19	Liaocheng Central Hospital	Xiting Zhang
20	The Affiliated Hospital of Qingdao University	Aijun Ma
21	Affiliated Hospital of Jining Medical University	Aimei Zhang
22	West China Hospital, Sichuan University	Bo Wu

Lu Y, *et al*. *Stroke Vasc Neurol* 2025;0:1–7. doi: 10.1136/svn-2024-003577

23	Shenzhen Second People's Hospital	Gelin Xu
24	Changzhou Wujin Traditional Chinese Medicine Hospital	Xiaoli Feng
25	The First Affiliated Hospital of Jinzhou Medical University	Yujie Jia
26	Xiangya Hospital, Central South University	Le Zhang
27	The First People's Hospital of Chenzhou/The First Affiliated Hospital of Xiangnan University	Jiping Yi
28	The Second Nanning People's Hospital	Zijun Wang
29	Beijing Shunyi Hospital	Mei Zhang
30	Wuhan No.1 Hospital	Zhangbao Guo
31	Shanghai Pudong New Area Gongli Hospital	Qiang Li
32	Dengzhou People’s Hospital	Guangliang Li
33	Pingyu People's Hospital	Feng Li
34	Chongqing Donghua Hospital	Yu Che
35	Jiujiang University Affiliated Hospital	Xiaoping Yin
36	Hengyang Central Hospital	Jing Ding
37	Xiuwu People's Hospital	Guangming Kang
38	Shimen People's Hospital	Kaoling Gong
39	The Fourth Affiliated Hospital of Soochow University	Yonggang Hao
40	Guanxian People's Hospital	Haijun Qiu
41	Benxi Central Hospital	Chengguang Song
42	Baotou Central Hospital	Baojun Wang
43	Xi'an International Medical Center Hospital	Hong Lin
44	Linfen Central Hospital	Wanying Li
45	Xinjiang Production&Construction Corps Hospital	Yan Xiao

46	The First Affiliated Hospital of Wenzhou Medical University	Beilei Zhu
47	General Hospital of Ningxia Medical University	Xiaolin Hou
48	Mengjin People's Hospital	Zhonghai Jia
49	The Sixth People's Hospital of Hengshui	Qin Zhang
50	Rudong People's Hospital	Jun Gu
51	Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine	Hao Zhang
52	The Affiliated Hospital of Xuzhou Medical University	Dunjing Wang
53	Shenzhen Hospital, Southern Medical University	Ming Hu
54	Zouping City People's Hospital	Xiao Wang
55	Luoning People's Hospital	Xiaomin Mei
56	Zibo Central Hospital	Ying Wang
57	The Eighth Medical Center of PLA General Hospital	Feng Qiu
58	Xinjiang Production and Construction Corps 13 Division Red Star Hospital	Haiying Teng

Supplemental Table 2. Definitions of outcomes

Event	Definition
Early neurological deterioration	New neurological symptoms or signs as well as the progression of existing neurological deficit symptoms or signs that occur within several hours or days of primary stroke onset, and will be judged based on any of the following criteria: (1) Total NIHSS score increases by ≥ 2 points; (2) NIHSS awareness score (1a to 1c) increases by ≥ 1 points; (3) NIHSS motor score (5a to 6b) increases by ≥ 1 points; (4) Any new neurological deficits not evaluated by NIHSS.
Stroke	Sudden symptoms and signs of acute neurological deficits, which are related to cerebral circulatory disorders and caused by focal or whole brain, spinal cord, or retinal vascular injury. Stroke includes ischaemic stroke and hemorrhagic stroke.
Ischaemic stroke	Acute focal cerebral or retinal infarction meeting any of the following criteria: (1) Clinical signs or imaging evidence of acute newly onset focal neurological deficits lasting more than 24 hours, excluding other non-ischaemic causes (such as brain infections, brain trauma, brain tumors, seizures, severe metabolic diseases, degenerative neurological diseases, and drug side effects); (2) Acute cerebral or retinal ischaemic events, excluding other non-ischaemic causes, with focal symptoms or signs lasting less than 24 hours, but

	accompanied by imaging evidence of new infarction; (3) Progression of original vascular ischaemic stroke (i.e., NIHSS increased ≥ 4 on the basis of primary ischaemic stroke, excluding hemorrhagic transformation after infarction or symptomatic intracranial haemorrhage) lasting longer than 24 hours, accompanied by new ischaemic lesion on brain MRI or CT. Etiological classification is based on the TOAST standard.
Hemorrhagic stroke	Acute focal or whole brain or spinal cord neurological dysfunction caused by non-traumatic brain parenchymal, intraventricular, and subarachnoid haemorrhage.
Symptomatic intracranial haemorrhage	Spontaneous and secondary (or therapeutic) bleeding, which meets the following three conditions at the same time: (1) Imaging evidence (brain CT or MRI) of any form of intracranial haemorrhage (including the Heidelberg standard 1a, 1b, 1c, 2, 3a, 3b, 3c, and 3d) confirmed by imaging doctors; (2) Deterioration of clinical symptoms: total NIHSS score increases by ≥ 4 points compared to the final score before worsening, or any item of NIHSS score increases by ≥ 2 points, or leads to tracheal intubation, decompressive bone flap removal, ventricular drainage, or other significant medical/surgical interventions; (3) No other reason to explain the worsening of clinical symptoms apart from intracranial haemorrhage.

Myocardial infarction	According to Third universal definition of myocardial infarction (Thygesen 2012), the term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for MI: 1. Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: (1) Symptoms of ischaemia. (2) New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB). (3) Development of pathological Q waves in the ECG. (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. (5) Identification of an intracoronary thrombus by angiography or autopsy. 2. Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3. Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5×99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of

	cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischaemia or (2) new ischaemic ECG changes or (3) angiographic findings consistent with a procedural complication or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. 4. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. 5. Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 × 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (1) new pathological Q waves or new LBBB, or (2) angiographic documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Vascular death	Death due to stroke, cardiac sudden death, acute myocardial infarction, heart failure, pulmonary embolism, cardiac/cerebrovascular intervention or surgery (unrelated to acute myocardial infarction), and other cardiovascular causes (such as arrhythmia irrelevant with sudden cardiac death, aortic aneurysm rupture, or peripheral arterial disease). Any death of unknown/unclear causes within 30 days after stroke, myocardial infarction, or cardio-cerebrovascular operation/surgery will be considered as death due to stroke, myocardial infarction, or cardio-

	cerebrovascular operation/surgery respectively.
Any bleeding events	Bleeding event is classified as mild, moderate and severe bleeding event based on Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Criteria: (1) Severe bleeding: Intracranial haemorrhage or bleeding causing hemodynamic changes and requiring blood transfusion or infusion, cardiotonic therapy, ventricular assist devices, surgery, or cardiopulmonary resuscitation to maintain sufficient cardiac output; (2) Moderate bleeding: Bleeding requiring blood transfusion but without hemodynamic changes requiring intervention; (3) Minor bleeding: Bleeding not requiring blood transfusion or infusion and without hemodynamic changes, including subcutaneous haemorrhage, small hematoma, or congestion spots at the puncture site, etc.
Antibiotic associated diarrhoea, enteritis, and constipation	Diarrhoea (loose or watery, mucous, bloody purulent, bloody stool, or the presence of lamellar or tubular pseudomembrane in the stool) with recent or current use of antibiotics, excluding other clear causes, including: (1) Various primary infectious diarrhoea, such as bacterial dysentery; (2) Organic intestinal diseases, such as inflammatory bowel disease; (3) Intestinal functional and allergic diseases; (4) Gastrointestinal surgery within 1 year, etc. Antibiotic associated diarrohea can be further divided into simple diarrhoea and antibiotic

	associated enteritis, such as mycotic colitis and pseudomembranous colitis (Clostridium difficile enteritis). Antibiotic associated constipation is defined as decreased stool frequency, decreased stool volume, dry stool, and exertion in defecation with recent or current use of antibiotics, excluding other organic or functional constipation with clear causes.
Inflammation-related biomarkers	NF-L, S100B, copeptin, sTrem2, sGPVI, sADAMTS 13, sCD40L, sP-selectin, MMPs, Claudin-5, SPP1, etc.

Supplemental Table 3. Study organization

Steering Committee
Yilong Wang, Yongjun Wang, Philip Bath, S. Claiborne Johnston, Pierre Amarenco, Fudong Shi, Ling Guan
Executive Committee
Yilong Wang, Ling Guan, Yao Lu, Baoshan Qiu, Lingling Jiang, Qianqian Yang, Meiyang Zhang, Dongyang Zhou, Chenhui Liu, Jianhua Li, Chen Xu
Data Safety and Monitoring Board
Jean-Paul Collet, Hao Li, David Wang
Statistical and Data Management Centre
Yuesong Pan, Luyan Wang, Ziyi Gao
Clinical Event Adjudication Committee
Hui Qu, Kehui Dong, Xiaoling Liao

Supplemental Table 4. **Previous clinical studies of minocycline applying on patients with acute ischaemic stroke**

PMID	Patients	Design	N	Age	NIHSS	Time window	Dosage of medication	Main outcomes
23105953	AIS	Open-label Non-randomised	89	>18	>1	< 6 h of onset	3, 4.5, 6, or 10mg/kg per 12h intravenously for 3d	IL-6 level at 24h NIHSS score at 90d
21737808	AIS	Open-label Non-randomised	104	>18	>1	< 6 h of onset	3, 4.5, 6, or 10mg/kg per 12h intravenously for 3d	MMP-9 level at 24h NIHSS score at discharge or 7d
17909152	AIS	Open-label Randomised	152	>18	>5	6-24h of onset	200mg per day orally for 5d	NIHSS, mRS, and BI score at 7, 30, 90d
22406775	First-ever AIS	Open-label Randomised	50	>18	>4	6-24h of onset	200mg per day orally for 5d	NIHSS, mRS, and mBI score at 1, 7, 30, 90d
23868273	Stroke (AIS 81%)	Open-label Randomised	95	≥18	≥1	< 24 h of onset	100mg per 12h intravenously for 2.5d	mRS and BI score at 90d NIHSS at 7d

NIHSS, National Institute of Health Stroke Scale; AIS, acute ischaemic stroke; mRS, modified Rankin Scale; BI, Barthel Index.