




# Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-II (TRACE II): rationale and design

Shuya Li <sup>1,2</sup> Bruce C V Campbell,<sup>3</sup> Lee H Schwamm,<sup>4</sup> Marc Fisher,<sup>5</sup> Mark Parsons,<sup>6</sup> Hao Li <sup>1</sup> Yuesong Pan <sup>1</sup> Yongjun Wang,<sup>1,2</sup> On behalf of the TRACE II investigators

**To cite:** Li S, Campbell BCV, Schwamm LH, *et al.* Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-II (TRACE II): rationale and design. *Stroke & Vascular Neurology* 2021;0. doi:10.1136/svn-2021-001074

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/svn-2021-001074>).

Received 23 April 2021

Accepted 2 August 2021

## ABSTRACT

**Background and purpose** Tenecteplase (TNK) is a promising agent for treatment of acute ischaemic stroke (AIS). We hypothesised that recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) is non-inferior to rt-PA in achieving excellent functional outcome at 90 days, when administered within 4.5 hours of ischaemic stroke onset.

**Methods and design** Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events (TRACE) is a phase III, multicentre, prospective, randomised, open-label, blinded-end point non-inferiority study. Patients eligible for intravenous thrombolysis therapy are randomised to rhTNK-tPA 0.25 mg/kg (single bolus) to a maximum of 25 mg or rt-PA 0.9 mg/kg (10% bolus +90% infusion/1 hour) to a maximum of 90 mg. Medications considered necessary for the patient's health may be given at the discretion of the investigator during 90-day follow-up.

**Study outcomes** The primary study outcome is excellent functional outcome defined as modified Rankin Scale (mRS) 0–1 at 90 days. Secondary efficacy outcomes include favourable functional outcome defined as mRS ≤2 at 90 days, ordinal distribution of mRS and major neurological improvement on the National Institutes of Health Stroke Scale. Safety outcomes are symptomatic intracranial haemorrhage within 36 hours and death from any cause.

**Discussion** There is no completed registration study of TNK in AIS worldwide. TRACE II strives to provide evidence for a new drug application for rhTNK-tPA in AIS within 4.5 hours through a well-designed and rigorously executed randomised trial in China.

**Trial registration number** NCT04797013.

## INTRODUCTION

The burden of stroke continues to increase worldwide. In China, stroke has become the leading cause of death, with ischaemic stroke being the dominant type.<sup>1–3</sup> Intravenous thrombolysis is of proven clinical benefit for eligible patients with acute ischaemic stroke (AIS) and recombinant tissue plasminogen activator (rt-PA) is the only licensed thrombolytic agent within 4.5 hours after symptom onset.<sup>4–6</sup>

Tenecteplase (TNK) is a genetically engineered modified form of rt-PA with practical delivery advantages and is currently approved to treat acute myocardial infarction (AMI) in many countries.<sup>7</sup> In China, Metalyse and recombinant human TNK tissue-type plasminogen activator for injection (rhTNK-tPA) are approved for AMI indication.<sup>8,9</sup> There is no completed registration study of TNK in AIS worldwide. Several phase II and III studies of TNK initiated by investigators provided information on its safety and efficacy for the treatment of AIS.<sup>10–14</sup> A meta-analysis of 5 randomised studies, including 1585 patients in total (828 TNK, 757 rt-PA), showed that the modified Rankin Scale (mRS) 0–1 at 90 days was 57.9% in TNK-treated patients vs 55.4% in rt-PA-treated patients with a risk difference of 4% (95% CI –1% to 8%). For safety end points, TNK and rt-PA demonstrated a risk difference of 0% in symptomatic intracranial haemorrhage (sICH, 95% CI –1% to 2%) and 90-day mortality (95% CI –3% to 2%).<sup>15</sup>

Although there is accumulating evidence supporting the use of TNK in patients with AIS, these data came from trials conducted in Caucasians. The optimal dosage of rhTNK-tPA for Chinese patients with AIS has not yet been demonstrated. A dose of 0.25 mg/kg may be suggested for future efficacy studies in Caucasians patients with AIS based on the results of contemporary clinical studies.<sup>4,12,13</sup> A phase II study of rhTNK-tPA in China showed that rhTNK-tPA was well tolerated in Chinese patients with AIS similar to the Caucasians at dosages of 0.25 mg/kg administered within 3 hours of symptom onset (results to be published). Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II (TRACE II), a phase III study, aiming to demonstrate that rhTNK-tPA 0.25 mg/kg is non-inferior to rt-PA 0.9 mg/kg for intravenous



© Author(s) (or their employer(s)) 2021. 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

Dr Yongjun Wang;  
yongjunwang@nrcnd.org.cn

thrombolysis of patients with AIS in China. The efficacy and safety results of this study may support a new drug application for rhTNK-tPA in AIS within 4.5 hours.

## METHODS

### Study organisation and design

The steering committee of TRACE II is the highest decision-making body and express opinions freely and independently at scheduled or unscheduled meetings (online supplemental file 1). It is responsible for

supervising the study executive. An independent data monitoring committee will maintain surveillance of participant safety and advise the steering committee about any safety concerns (table 1).

TRACE II is a phase III, multicentre, prospective, randomised, open-label, blinded-end point (PROBE) non-inferiority study.<sup>16</sup> Randomisation will be 1:1 for intravenous thrombolysis with rhTNK-tPA versus rt-PA via a centralised website. Investigational product should be administered no later than 4.5 hours after symptom

**Table 1** Trial assessment flow chart

Procedure/Investigation	Baseline	Treatment		Follow-up		Day 7±1 or discharge	Day 90±7
	–4.5 hours	0 hour	24±2 hours	24–36 hours			
Informed consent*	X						
Demographic data	X						
Symptoms of the disease	X						
Medical history†	X						
Prior medication	X						
Concomitant medication‡	X	X	X	X	X	X	X
Vital signs§	X	X	X			X	
mRS¶	X§						X
NIHSS	X		X			X	
Barthel Index							X
EQ5D							X
Pregnancy tests**	X						
Laboratory assessments††							
Haematology	X		X			X	
Clinical chemistry	X		X			X	
Coagulation profile	X		X			X	
Urinalysis			X			X	
ECG‡‡	X					X	
Imaging§§	X			X			
Randomisation	X						
Thrombolysis information‡		X					
Adverse events/Serious adverse events assessment		X	X	X	X	X	X

\*Patients who had symptoms on awakening or unknown onset were excluded in the study.

†Prior medication is recorded only for those drugs that need to be restricted in the eligibility criteria.

‡Thrombolysis information includes the time of thrombolytic therapy in both groups (including the intravenous bolus time, the starting and ending time of maintenance infusion, the dose of the bolus and the maintenance infusion, the adverse events); pay attention to collecting information of bridging treatment.

§The baseline blood pressure test is collected at the time of vital signs collection; The '0 hour' visit is regarded as within 5 min before thrombolysis; vital signs include blood pressure, pulse, temperature and breath.

¶The mRS scores screened into the group indicate preonset score.

\*\*Pregnancy test is limited to female subjects of childbearing age.

††Laboratory assessments: (1) baseline laboratory assessments include haematology, clinical chemistry and coagulation profile; no need to repeat the assessments performed after the attack and before thrombolysis. Fasting blood is required for the baseline lipid profile (total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides). Fast glucose is allowed to decide eligibility criteria with serum glucose collected synchronously. The clinical chemistry results are available after the administration of study drugs. The investigators will deal with the abnormal results according to guidelines and the clinical pathway if necessary. (2) The laboratory assessments of 72 hours after thrombolysis, including haematology, clinical chemistry, coagulation profile and urinalysis, can be acceptable for the 24 hours visit. (3) Haematology, clinical chemistry, coagulation profile and urinalysis should be done at 7±1 days or before discharge (whichever occurs first).

‡‡No need to repeat ECG after the attack and before thrombolysis.

§§The baseline imaging, whatever 'CT or MRI', is used to exclude intracranial haemorrhage. Imaging data from another hospital is accepted according to investigators. The follow-up imaging (CT or MRI) should be completed within 24–36 hours to detect intracranial haemorrhage.

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

onset. Patients will be followed up 90 days to assess the primary outcome. Approximately 70 stroke centres in China will participate. Estimated study duration is 32 months.

### Patient population

#### Inclusion criteria<sup>4 17</sup>

1. Age is  $\geq 18$  years.
2. AIS symptom onset  $\leq 4.5$  hours, onset time refers to the time the patient was last known to be well.
3. Prestroke mRS score  $\leq 1$ .
4. Baseline National Institutes of Health Stroke Scale (NIHSS) 5–25 (inclusive).
5. Informed consent from the patient or legally authorised representative.

#### Exclusion criteria

1. Intention to proceed to endovascular treatment.
2. Allergy to TNK or alteplase.
3. Rapidly improving symptoms at the discretion of the investigator.
4. NIHSS consciousness score (NIHSS 1a)  $> 2$ .
5. Arterial puncture at a non-compressible site within the previous 7 days, major surgery within the previous 14 days, severe trauma, gastrointestinal or urinary tract haemorrhage within the previous 21 days.
6. Myocardial infarction or ischaemic stroke in previous 3 months, previous ICH (including parenchymal haemorrhage, intraventricular haemorrhage, subarachnoid haemorrhage, subdural/external haematoma, etc), severe brain trauma, intracranial or intraspinal surgery in previous 3 months or known malignant intracranial neoplasm, giant intracranial aneurysm or arteriovenous malformation.
7. Persistent blood pressure elevation (systolic  $\geq 180$  mm Hg or diastolic  $\geq 100$  mm Hg), despite blood pressure-lowering treatment.
8. Blood glucose  $< 2.8$  mmol/L or  $> 22.22$  mmol/L (point-of-care glucose testing is acceptable).
9. Any known defect in coagulation, for example, current use of oral warfarin anticoagulant with an international normalised ratio  $> 1.7$  or prothrombin time  $> 15$  s, or heparins during the last 48 hours, or use of direct thrombin inhibitors or direct factor Xa inhibitors during the last 48 hours or with an elevated activated partial thromboplastin time greater than the upper limit of normal.
10. Known defect of platelet or clotting function, platelet count below  $100 \times 10^9$ /L (note that patients on antiplatelet agents can be included).
11. Weakness after witnessed or presumed seizure that cannot be explained by acute ischaemic injury on brain imaging.
12. Hypodensity in  $> 1/3$  middle cerebral artery territory on non-contrast computer tomography (NCCT).
13. ICH, subarachnoid haemorrhage or other brain haemorrhage identified by CT or MRI.

14. Any terminal illness such that patient would not be expected to survive  $> 1$  year.
15. Pregnant women, nursing mothers.
16. Inability to adhere to the trial protocol or follow-up.
17. Participation in another clinical trial within the previous 3 months.
18. Any condition that, in the judgement of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study.

### Baseline measures

Patients who are clinically suspected of AIS within 4.5 hours after symptom onset will be assessed for intravenous thrombolysis eligibility after CT scan. Demographics, medical history, current medications and baseline laboratory tests will be collected. Baseline neurological impairment (eg, NIHSS) and prestroke functional (eg, mRS) scores before this attack will be performed by a certified physician with uniform and standardised training. Primary or comprehensive stroke centres will be selected as study sites to make sure that patients can be assessed and treated with rapid workflow.

### Randomisation and blinding

The proportion of patients in the rhTNK-tPA group and the rt-PA group is 1:1 in each study site. Central web-based randomisation system (Randomization and Trial Supply Management V.3.1.2, Beijing Bioknow Information Technology, China) will be used for randomisation in dynamic blocks of four to balance distribution of group assignments at any time. The size of the blocks will be withheld from the investigators to make sure that they are unaware of the treatment assignments. The intravenous thrombolytic treatment is open label. Investigators who involved in the subsequent clinical and imaging assessment of outcomes are blinded to treatment allocation.

### Treatment intervention

#### Intervention group: rhTNK-tPA (0.25 mg/kg, max 25 mg)

rhTNK-tPA (0.25 mg/kg) is given as a single, intravenous bolus (over 5–10 s) immediately on randomisation. Maximum dose is 25 mg.

#### Control group: rt-PA (0.9 mg/kg, max 90 mg)

Ten per cent dose of rt-PA (0.9 mg/kg) is given as bolus and the remainder over 1 hour infusion. Maximum dose is 90 mg.

Patients for whom endovascular treatment is planned are excluded from this study. Patients who are subsequently judged to require endovascular treatment after intravenous thrombolysis in the judgement of the investigator will be included in the intention-to-treat analysis, but will be excluded from per-protocol analysis in order to avoid the effect on the outcome.

### Outcomes and follow-up

Study visits will be performed on the day of randomisation, at 24 hours and 24–36 hours after randomisation, at

day 7 and at day 90. On admission, CT with or without CT angiography (CTA) (or MRI/MR angiography (MRA)) is performed. At 24–36 hours after randomisation, CT, CTA with CT perfusion or MRA with diffusion-weighted magnetic resonance imaging (DW-MRI) is performed. At randomisation and during follow-up visits, including but not limited to clinical information will be collected: neurological evaluation (mRS and NIHSS); a physical examination, vital signs, concomitant medications and adverse events (AEs). Information is collected at a face-to-face consultation, mRS allows telephone interview (table 1).

Serious adverse events (SAEs) will be reported by investigators adhering to the protocol and Good Clinical Practice guidelines. Two members of the independent Clinical Events Committee (CEC) will adjudicate the report. SAEs and AEs will be tabulated using standard terminology.

### Primary outcome

Proportion of patients with excellent functional outcome defined as mRS score  $\leq 1$  point at 90 days.

### Secondary outcomes

#### Efficacy outcomes

1. Proportion of participants with mRS  $\leq 2$  at 90 days.
2. Ordinal distribution of mRS at 90 days.
3. Proportion of participants with improvement on NIHSS of  $\geq 4$  points or a score  $\leq 1$  at 24 hours and at 7 days or discharge (whichever occurs first).
4. Barthel Index score  $\geq 95$  at day 90.

#### Safety outcomes

1. sICH within 36 hours (as defined by Safe Implementation of Thrombolysis in Stroke<sup>18</sup> and The European Cooperative Acute Stroke Study III<sup>19</sup>).
2. Systemic bleeding at 90 days (as defined by The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries<sup>20</sup>).
3. Death from any cause within 90 days.
4. AEs/SAEs within 90 days.

### Clinical Events Committee

The CEC consists of experienced neurologists and cardiologists who are not involved in the execution of the study. Membership of the CEC (including qualifications, roles and responsibilities) shall be confirmed by the steering committee. Clinical end point events include: new vascular events, sICH, systematic bleeding and death. All clinical end points are first determined by the investigator, then verified and adjudicated by the CEC based on clinical symptoms, laboratory tests and imaging data.

### Data monitoring committee

An independent data monitoring committee (DMC) will protect the interests of the participants during the study. The DMC need to review the safety and efficacy data gathered during the study, especially serious unexpected adverse reactions, evaluate the risks and benefits regularly and dynamically, provide professional advice to the

steering committee based on the analysis results carried out by an independent statistician. A DMC Charter details roles, composition, responsibilities and procedures to ensure maintenance of independence and objectivity of the DMC (online supplemental file 2).

### Sample size and statistical analysis

#### Sample size

TRACE II uses a non-inferiority design with the primary efficacy outcome being the proportion of patients achieving mRS 0–1 at 90 days. Based on meta-analysis of previous trials, the risk ratio for the effect of rt-PA versus placebo for the outcome of mRS 0–1 was 1.24 (95% CI 1.14 to 1.36).<sup>21</sup> Prior data indicate that TNK is unlikely to be less safe or effective than alteplase and is more convenient. Under these circumstances, the Food and Drug Administration guidelines for non-inferiority design allow for a relaxation of non-inferiority criteria to preserve at least 50% of the effect of alteplase. In the TRACE trial, TNK will therefore be declared non-inferior if the lower 97.5% one-sided CI of the risk ratio for the primary outcome does not cross 0.937. The phase II TRACE study found that 59.4% of rt-PA-treated patients achieved mRS 0–1 at 90 days. The risk ratio boundary of 0.937 would therefore correspond to a 5.9% absolute risk difference between the rhTNK-tPA group and the rt-PA group. This 3.74% risk difference margin is regarded as acceptable by clinical experts. Assuming a power of 85%, a one-sided alpha level of 0.025 and an absolute relative risk of 1.07 (59.3% in rhTNK-tPA vs 63.6% in rt-PA group with mRS 0–1 at 90 days based on the TRACE data), the sample size for each group is 614 patients. Allowing for a loss-to-follow-up rate of 10%, the final sample size estimate is 1364 patients (682 in each treatment group).

#### Statistical analysis

The primary efficacy analysis will be on an intention-to-treat basis and compared using two-sided significance tests. Fisher's exact probability method or  $\chi^2$  test will be used for comparison of categorical variables, Wilcoxon rank-sum test for comparison of ordinal variables, T test or rank-sum test for comparison of continuous variables and mean difference of score with 95% CI will be calculated. The Cochran-Mantel-Haenszel  $\chi^2$  test considering the central effect will be used for comparison of primary end points between groups, and the 95% CI of OR was calculated. The odds of achieving mRS 0–1 at 90 days will be analysed using logistic regression with adjustment of baseline NIHSS and age. OR and the 95% CI will be reported. Per-protocol analysis will be performed according to whether bridging therapy was assigned. No interim analysis is planned in this trial. All statistical analyses will be performed using SAS V.9.4 software.

### DISCUSSION

As a major public health problem in the world, improving treatment of AIS deserves continuous effort. An improved intravenous thrombolytic approach could have a major



impact on health delivery. TNK is a genetically engineered modified form of rt-PA with better fibrin specificity, high resistance to plasminogen-activator inhibitor-1 and slower plasma clearance permitting bolus administration which may facilitate efficient institution of reperfusion therapy.

The TRACE II study excludes patients intended to have endovascular thrombectomy. Although several studies of direct endovascular thrombectomy have reported similar results with and without bridging alteplase in the subgroup of patients who present directly to an endovascular-capable centre, there is residual uncertainty about the best treatment approach and intravenous thrombolysis remains the recommended treatment for patients with AIS within 4.5 hours.<sup>22–25</sup> Previous studies reported that patients with AIS with large vessel occlusion (LVO) receiving intravenous thrombolysis with TNK having favourable clinical outcomes at 3 months compared with patients receiving intravenous alteplase.<sup>26–27</sup> Subgroup analysis of the patients with AIS with LVO will be conducted in TRACE II study. A separate TRACE III trial will focus to assess the effect of TNK for patients with AIS with LVO in the late time window (4.5–24 hours after stroke onset).

A double-blind design is considered optimal for phase III randomised controlled trials. However, a double-blind and double-dummy drug administration would significantly increase the complexity of the trial procedure in the very narrow time window and delaying drug administration for patients with AIS is unethical. A PROBE design was therefore chosen for TRACE II. Although some investigators in the local centres may be aware of the treatment allocation, investigators who are involved in the subsequent clinical and imaging assessment of outcomes are blinded to treatment allocation.

The most common AEs in clinical studies of thrombolytic agents are haemorrhage, including ICH and systemic bleeding. The safety profile of TNK appears similar to alteplase and TRACE II uses standard thrombolytic therapy exclusions to reduce the risk of bleeding. Angio-oedema can occur with both TNK and alteplase and is managed according to standard treatment guidelines. No patients developed angio-oedema in the TRACE phase II study.

In conclusion, TRACE II addresses a critical clinical question in patients with ischaemic stroke. Demonstration of non-inferiority of TNK in this trial would support implementation of convenient intravenous thrombolysis with TNK for patients with AIS.

#### Author affiliations

<sup>1</sup>China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

<sup>2</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

<sup>3</sup>Department of Medicine and Neurology, University of Melbourne, Melbourne, Victoria, Australia

<sup>4</sup>Department of Neurology and Comprehensive Stroke Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

<sup>5</sup>Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

<sup>6</sup>Department of Neurology, Liverpool Hospital, South Western Sydney Clinical School, Sydney, New South Wales, Australia

**Acknowledgements** The authors extend their special thanks to the physicians as well as all other personnel who dedicated themselves to the TRACE II study. The Steering Committee: Yongjun Wang, Bruce CV Campbell (AUS), Lee H Schwamm (USA), Marc Fisher (USA), Mark W Parsons (AUS). Data Monitoring Committee: Hao Li, David Wang (USA), Lawrence Wong (HK), Dongsheng Fan, Magdy Selim (USA). Independent statistician: Yuesong Pan. Clinical Events Committee: Wenli Hu, Yonghua Huang, Lv Qiang.

**Contributors** Obtained funding, concept and design: YW. All authors contributed to the study design. Drafting of the manuscript: SL. Critical revision of the manuscript for important intellectual content: BCVC, LHS. Statistical analysis: HL, YP. All authors critically reviewed the manuscript and approved the submitted version.

**Funding** This study is supported by the National Natural Science Foundation of China (81870905), the National Key R&D Program of China (2017YFC1308204) and the National Science and Technology Major Project (2017ZX09304018). This study was sponsored and funded by Guangzhou Recomgen Biotech Co., Ltd.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki. All participants gave informed consent before taking part. This study obtained Ethics approval of Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University with number YW2020-046-04.

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

**Data availability statement** Data are available on reasonable request. None.

**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/>.

#### ORCID iDs

Shuya Li <http://orcid.org/0000-0002-7263-0365>

Hao Li <http://orcid.org/0000-0002-8591-4105>

Yuesong Pan <http://orcid.org/0000-0003-3082-6789>

#### REFERENCES

- GBD 2016 Lifetime Risk of Stroke Collaborators, Feigin VL, Nguyen G, *et al.* Global, regional, and Country-Specific lifetime risks of stroke, 1990 and 2016. *N Engl J Med* 2018;379:2429–37.
- Zhou M, Wang H, Zeng X, *et al.* Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the global burden of disease study 2017. *The Lancet* 2019;394:1145–58.
- Wang Y-J, Li Z-X, Gu H-Q, *et al.* China stroke statistics 2019: a report from the National center for healthcare quality management in neurological diseases, China national clinical research center for neurological diseases, the Chinese stroke association, National center for chronic and non-communicable disease control and prevention, Chinese center for disease control and prevention and Institute for global neuroscience and stroke collaborations. *Stroke Vasc Neurol* 2020;5:211–39.
- Powers WJ, Rabinstein AA, Ackerson T, *et al.* Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2016 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2019;50:e344–418.
- Emerson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–35.
- Liu L, Chen W, Zhou H, *et al.* Chinese stroke association guidelines for clinical management of cerebrovascular disorders: Executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. *Stroke Vasc Neurol* 2020;5:159–76.
- Llavadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001;286:442–9.
- Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van De Werf F, Adgey J, *et al.* Single-bolus tenecteplase compared with front-loaded alteplase in acute

- myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716–22.
- 9 Wallentin L, Goldstein P, Armstrong PW, *et al.* Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 2003;108:135–42.
  - 10 Parsons M, Spratt N, Bivard A, *et al.* A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012;366:1099–107.
  - 11 Huang X, Cheripelli BK, Lloyd SM, *et al.* Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol* 2015;14:368–76.
  - 12 Campbell BC, Mitchell PJ, Churilov L, *et al.* Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. *Int J Stroke* 2018;13:328–34.
  - 13 Campbell BCV, Mitchell PJ, Churilov L, *et al.* Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK Part 2 randomized clinical trial. *JAMA* 2020;323:1257–65.
  - 14 Logallo N, Novotny V, Assmus J, *et al.* Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol* 2017;16:781–8.
  - 15 Burgos AM, Saver JL. Evidence that tenecteplase is Noninferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. *Stroke* 2019;50:2156–62.
  - 16 Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (probe) study. A novel design for intervention trials. *Blood Press* 1992;1:113–9.
  - 17 Berge E, Whiteley W, Audebert H, *et al.* European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;6:I–LXII.
  - 18 Wahlgren N, Ahmed N, Dávalos A, *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in Stroke-Monitoring study (SITS-MOST): an observational study. *Lancet* 2007;369:275–82.
  - 19 Hacke W, Kaste M, Bluhmki E, *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–29.
  - 20 Berkowitz SD, Granger CB, Pieper KS, *et al.* Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. the global utilization of streptokinase and tissue plasminogen activator for Occluded coronary arteries (GUSTO) I Investigators. *Circulation* 1997;95:2508–16.
  - 21 Emberson J, Lees KR, Lyden P, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–35.
  - 22 Yang P, Zhang Y, Zhang L, *et al.* Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
  - 23 Nogueira RG, Tsivgoulis G. Large vessel occlusion strokes after the DIRECT-MT and SKIP trials: is the alteplase syringe half empty or half full? *Stroke* 2020;51:3182–6.
  - 24 Goyal M, Menon BK, van Zwam WH, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
  - 25 Goyal M, Almekhlafi M, Dippel DW, *et al.* Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions. *Stroke* 2019;50:645–51.
  - 26 Katsanos AH, Safouris A, Sarraj A, *et al.* Intravenous thrombolysis with tenecteplase in patients with large vessel occlusions: systematic review and meta-analysis. *Stroke* 2021;52:308–12.
  - 27 Psychogios K, Palaodimou L, Katsanos AH, *et al.* Real-world comparative safety and efficacy of tenecteplase versus alteplase in acute ischemic stroke patients with large vessel occlusion. *Ther Adv Neurol Disord* 2021;14:1756286420986727.

---

铭康 TNK-III 期

# Academic Steering Committee

## Charter

Version 1.0

(manuscript) (2021.2.21)

*Confidential*

1

Content

Chapter I General Provisions .....3

Chapter II Organizational Structure.....4

Chapter III Functions and Powers .....5

Chapter IV Rules of Procedure .....6

Chapter V Supplementary Provisions.....8



## Chapter I General Provisions

**Article 1** In order to strengthen the construction of clinical study steering committee, improve the management structure of clinical study, and ensure the effective role of experts in ethics, clinical practice, and biostatistics in clinical study, the Charter of Association is formulated in accordance with the relevant guiding principles of ICH-GCP and NMPA and in consideration of the actual situation of clinical study projects.

**Article 2** The Academic Steering Committee of Clinical Research (hereinafter referred to as the "Steering Committee") is the highest decision-making body and academic institution of clinical study. It is responsible for promoting science and democracy, ensuring the standard of clinical study decision-making, scientifically organizing, coordinating and exercising the functions and powers of making decisions on major matters of clinical study affairs.

**Article 3** All participants in the clinical study must respect and support the independent exercise of functions and powers of the steering committee, and provide necessary conditions for the normal work of the steering committee.

**Article 4** The Steering Committee should follow the laws of clinical study under the relevant principles of ICH-GCP and NMPA, and respect the freedom of study and academic equality. Through clinical study to encourage scientific study innovation, promote scientific study development and personnel training, improve the quality of scientific study; To perform their duties fairly, justly and openly; Protect the interests of patients; To ensure that researchers, laboratory personnel, biostatistics, supervision and other study participants play an active role in scientific study and academic affairs, and promote the scientific development of clinical study in China.

## Chapter II Organizational Structure

### Article 5 Functions of the Steering Committee:

Chairman: 1 person

Vice-chairman: 1 person

Committee member: 3 person

External spokespersons: 1 person

Secretary of Steering Committee: 1 person

**Article 6** Members of the steering committee should meet the following requirements:

- (1) Comply with relevant Chinese laws and regulations; Follow the ICH-GCP and NMPA guidelines;
- (2) Respect science; High academic attainments and high academic reputation;
- (3) Correct style of study and rigorous scientific study;
- (4) Fair and upright, strong sense of responsibility;
- (5) They should perform their duties normally.

**Article 7** A member of the Steering Committee may be removed or agree to resign after discussion and decision of the plenary meeting of the Steering Committee under any of the following circumstances during his term of office:

- (1) To apply for resignation from the committee on one's own initiative;
- (2) Unable to perform duties due to reasons such as health, age or change of position;
- (3) Being lazy in performing his duties or violating his obligations as a member;
- (4) Violating laws, professional ethics or academic misconduct;
- (5) Unable or unfit to hold the post due to other reasons.

### Chapter III Functions and Powers

**Article 8** The members of the steering committee should enjoy the following rights:

- (1) Know the information and operation structure related to the clinical study;
- (2) Inquiring relevant parties on study matters;
- (3) Express opinions freely and independently at meetings of the Steering Committee, and to discuss, consider and vote on resolutions;
- (4) Make suggestions on and supervise the work of study Services and other committees, such as the DMC;
- (5) Other rights provided for in the Charter of Association.

**Article 9** The members of the steering committee should perform the following obligations:

- (1) Abide by the Constitution, laws and regulations of the country, observe academic norms and strictly observe academic ethics;
- (2) Abide by the Charter of Association of the Steering Committee, adhere to the academic and professional judgment, and justly perform their duties;
- (3) Diligent and due diligence, and actively participate in the meetings of the steering committee and relevant activities; Strictly keep confidential matters, and should not entrust others to participate in the decision-making of the steering committee;
- (4) Other obligations stipulated in the Charter of Association.

**Article 10** The main duties of the steering committee are as follows:

- (1) Review Trial Master File (TMF) documents such as clinical study protocol, case report form, informed consent, study medical record, investigator brochure, etc.;
- (2) Nominate and review the Constitution of the Data Monitoring Committee (DMC);
- (3) Deliberate, demonstrate and put forward guiding opinions on clinical study related subject application, platform construction, operation management, etc.
- (4) Review DMC report and Clinical Study Reports(CSR);
- (5) Make suggestions and decisions on clinical study related results declaration, article publication, conference papers, news publicity, etc.;
- (6) Evaluate the AE or SAE associated with the study;
- (7) Other duties assigned by the Charter of Association.

## Chapter IV Rules of Procedure

### Article 11 Meeting plan:

- (1) Kick-off meeting: The purpose is to familiarize the members of the academic committee with the study project background, work process and their respective responsibilities, and to review and approve the academic committee charter.
  - Start-up meeting time: before the first subject is enrolled in the group.
  - The agenda of the kick-off meeting includes: clarifying responsibilities, discussing and finalizing the constitution of the academic committee; determining the meeting and schedule of the academic committee to be held; other regular transactional work, etc.
- (3) Planned audit/monitor meeting
  - Meeting conditions and frequency: Regularly hold academic committee meetings to conduct event analysis.

- Meeting review content: understand the specific information of each group's baseline characteristics, occurrence of adverse events, etc.
- (4) Unplanned meetings: According to work needs or events trigger, upon the proposal of the chairman or vice-chairman of the steering committee, or a joint proposal of more than 1/3 of the members, a temporary plenary meeting of the steering committee can be convened to discuss and review related matters.

**Article 12** A plenary meeting of the Steering Committee should, in principle, be held only when more than two-thirds of the members are present. The meeting should be presided over by the chairman. If the chairman is unable to preside over the meeting for some reason, he may entrust the vice-chairman to preside over the meeting.

**Article 13** The chairman of the steering committee may preside over a meeting of directors to discuss the daily work of the steering committee according to the needs of the work. The members of the Council of Directors should be composed of a chairman, vice-chairmen and a secretary.

**Article 14** The Steering Committee should adopt the principle of majority rule in matters decided by the minority. Voting on major matters should be approved only with the consent of more than two-thirds of the members attending the meeting.

**Article 15** The matters decided by the Steering Committee should generally be voted by secret ballot, or by show of hands or secret ballot at the choice of the moderator according to the nature of the matters. In case of an urgent matter requiring a vote, the voting may be conducted by communication upon the agreement of the meeting of the chairmen of the steering committee.

**Article 16** When the Steering Committee deliberates and evaluates matters related to the interests of the members themselves, the relevant members should withdraw. The chairman of the committee should decide whether the withdrawal is necessary.



## **Chapter V Supplementary Provisions**

**Article 17 The steering committee is responsible for the interpretation of the Charter of association.**

**Article 18 The Charter of Association should be promulgated and implemented after deliberation at the first meeting of the Steering Committee.**

DMC 铭康 TNK-III 期

V1.0 2021-02-04

## Data Monitoring Committee (DMC ) Charter

**Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II**  
—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

(edition V1.0/2021.02.04)

**Investigation drug: Recombinant human TNK tissue-type plasminogen activator for injection**

**Sponsor: Guangzhou Recomgen Biotech Co., Ltd.**

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

## DMC charter signing page

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Guangzhou Recomgen Biotech Co., Ltd.

Signature of the sponsor

Representative of the Sponsor:

Signature:

Date:

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

## DMC charter signing page

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Signed by the Chairman of the Clinical Trial Data Safety  
Monitoring Committee

The chairman of the DMC:

Signature:

Date:

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

## DMC charter signing page

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Signed by members of the Clinical Trial Data Safety  
Monitoring Committee

DMC member:

Signature:

Date:

## DMC charter signing page

---

*Confidential*



DMC 铭康 TNK III 期

V1.0 2021-02-04

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Signed by members of the Clinical Trial Data Safety  
Monitoring Committee

DMC member:

Signature:

Date:

**DMC charter signing page**

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Signed by members of the Clinical Trial Data Safety  
Monitoring Committee

DMC member:

Signature:

Date:

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

## DMC charter signing page

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Signed by members of the Clinical Trial Data Safety  
Monitoring Committee

DMC member:

Signature:

Date:

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

## DMC charter signing page

Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours

**I agree and fully understand the circumstances set out in the Charter. I will discharge my duties strictly in accordance with the rules and regulations, and any operation against the rules will be deemed invalid.**

Signed by independent statistician of clinical trial data safety  
Monitoring committee

DMC independent statistician:

Signature:

Date:

---

*Confidential*

DMC 铭康 TNK III 期

V1.0 2021-02-04

## Directory

<b>I. STUDY OVERVIEW AND OBJECTIVES .....</b>	<b>1</b>
1. STUDY OBJECTIVES .....	2
2. STUDY DESIGN .....	4
3. INTRODUCTION TO THE DMC .....	4
<b>II. COMPOSITION OF DMC .....</b>	<b>5</b>
1. CHAIRMAN AND MEMBERS OF THE DMC .....	5
2. DMC SUPPORT GROUP .....	5
<b>III. INDEPENDENCE OF DMC .....</b>	<b>6</b>
<b>IV. DMC RESPONSIBILITIES .....</b>	<b>7</b>
1. MAIN RESPONSIBILITIES .....	7
2. RESPONSIBILITIES OF THE CHAIRMAN .....	8
3. RESPONSIBILITIES OF THE DMC .....	8
4. RESPONSIBILITIES OF THE SPONSOR .....	8
5. RESPONSIBILITIES OF THE SUPPORT TEAM .....	9
<b>V. DMC MEETING .....</b>	<b>9</b>
1. DMC MEETING FORM .....	10
2. DMC MEETING PLAN .....	10
<b>VI. STATISTICAL ANALYSIS AND RESULTS .....</b>	<b>12</b>
1. CONTENTS OF STATISTICAL ANALYSIS .....	12
2. ACCESS TO ANALYSIS RESULTS .....	12

---

*Confidential*



DMC 铭康 TNK III 期	V1.0 2021-02-04
<b>VII. EXCHANGE AND COMMUNICATION .....</b>	<b>13</b>
1. DATA DELIVERY .....	13
2. MINUTES OF DMC MEETINGS.....	13
3. DMC PROPOSAL .....	14
<b>VIII. ARCHIVING OF DOCUMENTS AND MATERIALS .....</b>	<b>15</b>
<b>IX. AMENDMENT OF DMC CHARTER .....</b>	<b>15</b>

Confidential

DMC 铭康 TNK III 期

V1.0 2021-02-04

---

**I. INTRODUCTION OF STUDY OVERVIEW AND OBJETIVES**

1. STUDY OBJETIVES

DMC 铭康 TNK III 期

V1.0 2021-02-04

**Primary objectives:**

To estimate the difference of proportion of subjects with excellent functional outcome defined as mRS score  $\leq 1$  point at 90 days between recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA)(0.25 mg/kg) and alteplase (0.9 mg/kg) in acute ischemic stroke within 4.5 hours.

**Secondary objectives:**

**1. To estimate the efficacy of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA)(0.25 mg/kg) and alteplase (0.9 mg/kg) in acute ischemic stroke within 4.5 hours for the following efficacy endpoints :**

- ① Proportion of subjects with mRS  $\leq 2$  point at 90 days.
- ② Ordinal distribution of mRS at 90 days.
- ③ Proportion of subjects with improvement on NIHSS of  $\geq 4$  points or a score  $\leq 1$  (whichever occurs first) at 24 h, 7 days or discharge.
- ④ Quality of life at 90 days (EQ-5D)
- ⑤ Proportion of Bathel index  $\geq 95$  at 90 days

**2. To estimate the safety of recombinant human TNK tissue-type plasminogen activator (rhTNK-tPA)(0.25 mg/kg) and alteplase (0.9 mg/kg) in acute ischemic stroke within 4.5 hours:**

- ① Symptomatic intracranial hemorrhage within 36 hours (as defined by ECASS III).
- ② Symptomatic intracranial hemorrhage within 90 days (as defined by ECASS III).
- ③ PH2 type of intracranial hemorrhage within 90 days (as defined by SITS).
- ④ Any intracranial hemorrhage bleeding at 90 days (as defined by GUSTO) .
- ⑤ Any extracranial hemorrhage bleeding at 90 days (as defined by GUSTO) .

---

Confidential

3

- ⑥ Deaths from any cause within 90 days.

DMC 铭康 TNK III 期

V1.0 2021-02-04

⑦ Adverse events (AEs)/ serious adverse events (SAEs) within 90 days.

## 2. STUDY DESIGN

This study is to evaluate the efficacy and safety of rhTNK- tPA (0.25 mg/kg) versus standard rt-PA (0.9mg/kg) in the treatment of hyperacute ischemic stroke (onset <4.5h). This is a phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial.

The drug administration method of the test drug (rhTNK-tPA) is as follows:

rhTNK-tPA (0.25mg/kg) is given as a single, intravenous bolus (over 5-10 seconds) immediately upon randomization. Maximum dose 25mg.

The administration method of positive control drug (rt-PA) is as follows: 10% dose of rt-PA (0.9 mg/kg) is given as bolus and the remainder over 1 hour. Maximum dose 90mg.

The target population of this study is patients with acute ischemic stroke (<4.5h after onset). Considering the benefit of subjects, intravenous thrombolytic therapy should be given as soon as possible after the onset, in order to achieve vascular recanalization or reperfusion and obtain a better prognosis. Due to the different administration methods of investigation drug and positive control drug, the double-blind double-dummy design will significantly increase the complexity of the procedure in the very narrow time window. The delay of drug administration for acute ischemic stroke patients may introduce ethical issues. Therefore, this study adopts the form of open design. To minimize bias, investigators who involved in the subsequent clinical and imaging assessment of outcomes are blinded to treatment allocation.

## 3. INTRODUCTION TO THE OBJETIVES OF DMC

In order to ensure the objectivity of subjects interests and data, on the basis of the study protocol calls for, for the Guangzhou Recomgen Biotech Co., Ltd. for " Tenecteplase Reperfusion therapy in Acute ischemic Cerebrovascular Events-II—A phase 3, multicenter, prospective, randomized, open label, blinded-endpoint (PROBE) controlled trial of recombinant human TNK tissue-type plasminogen activator (rhTNK- tPA) for injection versus alteplase for acute ischemic stroke within 4.5 hours", The Data Monitoring Committee (DMC) is initiated by China National Clinical Research Center for Neurological Diseases to analyze

DMC 铭康TNK III 期

V1.0 2021-02-04

and review the clinical study data, with the aim of ensuring the safety of the subjects in the clinical trial, the rationality and scientific value of the continued trial.

The DMC, independent of the sponsor, provides professional advice to protect the interests of the subjects and to evaluate the safety of the test drug during the study. The main objectives of this DMC are as follows:

- Periodically evaluate subject safety;
- Periodically evaluate the implementation of the study.

DMC will provide DMC proposal to the sponsor based on the analysis results, and the sponsor will ultimately decide to accept or reject the DMC proposal. All decisions should be made in accordance with the Practice for Good Clinic Practice (GCP), the Helsinki Declaration and relevant national or international regulations to ensure the best safety and interests of the subjects.

## II. COMPOSITION OF DMC

### 1. CHAIRMAN AND MEMBERS OF THE DMC

The DMC consists of a chairman and four committee members. DMC members are all senior clinicians with relevant disease expertise and statisticians familiar with study design, and have no significant conflict of interest with this study. The names and contact details of the DMC members are shown in Appendix 1.

The chairman of DMC is recommended by the sponsor and is fully responsible for the operation of DMC.

### 2. DMC SUPPORT GROUP

Independent statisticians: Since the DMC may need to review the analysis results of non-blind data, in parallel with the establishment of the DMC, independent statisticians or an independent statistical team (statisticians and statistical programmers) should be established to support the work of the DMC. The independent statistical team must be independent of the relevant personnel (in addition to the DMC, including the sponsor, the investigator, the contract research organization, the ethics committee, etc.), especially when data blindness is involved. In principle, for clinical trials where data blindness is required, the independent statistical team is

DMC 铭康TNK III 期

V1.0 2021-02-04

only responsible for providing DMC the non-blind data and analysis results, and should not disclose the non-blind information to any other people, institutions or organizations.

The independent statistical analysis of this project will be carried out by an independent statistician, who will conduct statistical analysis on the collected data and prepare data analysis reports for DMC according to the preset statistical analysis plan and the requirements of DMC. Independent statisticians have no decision-making and voting rights in DMC meetings.

Administrative assistant: DMC requires an administrative assistant who is independent of the study parties to undertake administrative coordination, logistics meetings, etc. Administrative assistant does not have the right to vote in DMC decisions.

The complete contact information for DMC support team members can be found in Appendix 2.

### III. INDEPENDENCE OF DMC

The independence of the DMC is crucial. Objectively reviewing the data helps to protect the integrity of the study and reduce bias in the results. DMC members should not serve on the project study team or serve as consultants and should maintain only necessary contact with the sponsor.

In reality, it is difficult to guarantee that DMC is completely independent from the sponsor, but the influence of non-independent factors on the study should be minimized as far as possible.

DMC members should avoid, as far as possible, conflicts of interest from finance, academic papers related to data from this study, and other aspects.

Financial Conflicts of Interest: Generally, a person who has a financial interest in a sponsor or competitor is considered to have a potential financial conflict of interest and should not participate in the work of the DMC. In addition, DMC members may also be involved in conflicts of interest if they receive more than reasonable remuneration for their services from sponsors.

Academic Conflicts of Interest: If some scholars have a predetermined view of the study

DMC 铭康 TNK III 期

V1.0 2021-02-04

project, they may not be able to objectively evaluate the monitoring content and should not be involved in DMC work. The independence of the DMC may also be affected if a member of the DMC is or will be the lead author of a published paper related to the study.

Other Conflicts of Interest: When a DMC member is an external consultant hired by the regulator, he/she should recuse himself/herself from the review of a drug product that is directly related to the study.

All candidate DMC members should, prior to the establishment of the DMC, report to the sponsor or the sponsor's client any information that may be considered as a conflict of interest so that the sponsor can determine whether or not they are suitable for the role of DMC member.

Any potential conflict of interest involving a member of the DMC after the official operation of the DMC should be immediately disclosed to the DMC and the sponsor for appropriate action, including withdrawal, replacement and election of a member of the DMC.

#### **IV. DMC RESPONSIBILITIES**

##### **1. MAIN RESPONSIBILITIES OF THE DMC**

In order to protect the interests of the study subjects and improve the integrity and reliability of study, the DMC need to review the efficacy and safety data gathered during the clinical study, and perform periodic or temporary motions of risk - benefit evaluation, from the safety, efficacy, quality of study operation, trial design adjustment, etc for the sponsor is as planned to continue after modifications, to continue or terminate or suspend all or a group of test proposal, and whether its proposal has been accepted by the sponsor.

- (1) Review materials such as protocol and analysis plan.
- (2) Assess the safety of the cumulative data from ongoing clinical trials to ensure the safety of subjects.
- (3) Evaluate the efficacy of the cumulative trial data (if appropriate) according to the predefined statistical principles.
- (4) Monitor the study implementation, including overall and center inclusion, protocol violations, baseline characteristics, etc.
- (5) Monitor the accuracy, completeness and timeliness of data.



DMC 铭康 TNK III 期

V1.0 2021-02-04

- (6) Monitor the compliance of investigator and participants to the protocol.
- (7) Review all relevant documents of DMC.
- (8) During the process of the study, consider the influence of external information on the study: such as the publication of relevant results of other studies or the progress of treatment that may affect the safety of subjects or the ethics of the study (DMC members are not responsible for collecting such information, which should be provided by the sponsor and the investigator).
- (9) Only DMC members can review non-blind clinical data and participate in the closed discussion of non-blind data.
- (10) To propose the sponsor to continue, modify, suspend or terminate the study.
- (11) Confidentiality of clinical trial data and discussion of DMC.

## 2. RESPONSIBILITIES OF THE CHAIRMAN OF THE DMC

- (1) Voting rights.
- (2) Organize meetings, assist in planning agendas, and ensure meeting minutes and recommendations are properly archived.
- (3) Summarize and facilitate discussion, and make the final vote when there is disagreement in the vote.
- (4) The main contact person of DMC.
- (5) Review and approve the DMC charter.
- (6) Ensure that the DMC voting process excludes managers associated with the study.
- (7) Discuss the DMC proposal with the sponsor and project team members.

## 3. RESPONSIBILITIES OF THE DMC

- (1) Voting rights.
- (2) Review and approve the DMC charter.
- (3) Discuss the DMC proposal with the sponsor and research team.

## 4. RESPONSIBILITIES OF THE SPONSOR

- (1) Select and approve the chairman and members of the DMC.
- (2) Review and approve the DMC charter.

DMC 铭康 TNK III 期

V1.0 2021-02-04

- (3) Review and implement DMC recommendations (if appropriate).
- (4) Sponsor staff, such as project leaders, investigator and other relevant staff, can attend open section of DMC meetings. All sponsors will attend only as observers, and the project leaders can comment on project content and government regulatory matters.
- (5) Communicate DMC recommendations with the investigator or relevant personnel, and notify regulatory authorities and other agencies if necessary.
- (6) Review information related to conflict of interest, and have the right to take action on conflict of interest found.
- (7) Solicit and arrange DMC tel meeting (or Sponsor's designated).
- (8) Send relevant documents to the DMC members (or the Sponsor designated).
- (9) Do not attend close meetings and do not discuss data with non-blind members.
- (10) Provide data and reports to DMC one week before the scheduled meeting (non-blind reports will be sent directly by the non-blind statistician to the chairman of DMC to ensure that confidential data will not be disclosed to any personnel of the sponsor).
- (11) Coordinate and provide DMC temporary application report in time.
- (12) Pay the accommodation and travel expenses of DMC members. In addition, meeting expenses should be recorded in the form of <XXXX/ person/time >.

## 5. RESPONSIBILITIES OF THE SUPPORT TEAM

Independent statistician: responsible for the analysis of the data (unblinded and blinded), participate in the open and close meetings of the DMC, explain the analysis report, participate in the discussion, but do not have the right to vote, he/she is the only person other than a member of the DMC who has access to the unblinded data, also need to sign a confidentiality agreement.

Administrative assistant: Prepare related materials for DMC, contact database to communicate, obtain and summarize information from all personnel; Provide logistic support and meeting affairs for DMC meeting.

## V. DMC MEETING

DMC 铭康 TNK III 期

V1.0 2021-02-04

## 1. DMC MEETING FORM

The format of the meeting may include open meeting and close meeting. Open meeting can invite relevant experts and sponsors to attend, whereas close meeting only DMC members and DMC invited personnel to attend.

Meetings can be face-to-face, tel meeting, or online, but keep them confidential.

### (1) Open meetings

Subject recruitment, data quality, compliance, and other issues that may affect the conduct and outcome of the study are discussed primarily in a blind setting. Sponsors can talk to DMC members about the study implementation process, present study background information, and answer questions from the DMC. Data that can be discussed at open meetings include inclusion, baseline characteristics, exclusions, and data management. The chairman or other DMC member takes minutes of the meeting in which all participants are listed and maintained by the DMC Support Group until the study completes. Open meeting participants may include investigator and other related person in addition to sponsor representatives, DMC and members of the independent statistical team, if required. The open meeting is hosted by the sponsor or DMC.

### (2) Close meetings

It is attended by DMC members and relevant personnel from independent statistical teams. At the meeting, independent statistical teams of statisticians provide unblind data analysis results. The DMC reviews the data and results and makes recommendations for continuing, terminating, or modifying the study design based on a predetermined plan. The meeting should be chaired by the Chairman of the DMC or a person designated by the Chairman. At the same time, the chairman or other DMC member should take minutes of the meeting, in which all participants should be listed.

## 2. DMC MEETING PLAN

### (1) A kick-off meeting

The objectives is to familiarize DMC members with the background of the study, DMC

DMC 铭康 TNK III 期

V1.0 2021-02-04

work procedure and their responsibilities, as well as review and approve the DMC charter.

The time: before the first subject was enrolled.

The agenda of the kick-off meeting includes: learning about the study products; Familiarize and review the study protocol; Define DMC responsibilities, discuss and finalize DMC charter; Discuss the format and content of the analysis report; Determine DMC meetings and schedules; The time limit for submitting the analysis report to the DMC prior to the DMC meeting; Management of meeting minutes; Other routine work, etc.

(2) Planned review/monitoring meeting

① Meeting conditions and frequency: audit and supervision meetings are held regularly, and safety analysis is conducted by DMC.

② Audit content of the meeting: DMC will listen to the report of independent statisticians in a non-blind state to understand the baseline characteristics of each group, the occurrence of adverse events and other specific information.

(3) Unplanned meetings

In addition to the planned data review meeting, the sponsor may request an unplanned DMC meeting to review the safety data and may provide additional test-related safety information to the DMC. Such meetings are particularly common when sponsors find urgent security issues.

The DMC may also convene unplanned meetings as it deems necessary, including the addition of unplanned statistical analysis. The DMC reserves the right to inform the sponsor of any information about an unscheduled meeting. If the sponsor needs to be informed, the DMC should explain to the sponsor the reason for holding the meeting, but care should be taken to avoid the risk of blinding and not to provide the sponsor with information that may bias the study results or affect the integrity of the trial.

(4) Quorum and participants of the meeting

Attendees include all DMC members and independent statisticians, the sponsor's decision-making management and research team (except close meetings) and administrative

DMC 铭康TNK III 期

V1.0 2021-02-04

assistants (except closed meetings). The five members of DMC should be the legal participants and the meeting attended by all five members should be considered as a valid meeting.

## VI. STATISTICAL ANALYSIS AND RESULTS

### 1. CONTENTS OF STATISTICAL ANALYSIS

All statistical analyses were conducted using SAS9.4 or higher statistical software and according to the prespecified statistical analysis plan.

Analysis content: actual number of subjects includes in each group, cases of inclusions and exclusion, demographic and other baseline characteristics, compliance and safety analysis. Statistical analysis included but was not limited to (1) the number of cases completed in each study center and the shedding of cases; (2) Analysis of demographic and baseline characteristics of each group at the time of inclusion; (3) Safety evaluation includes the comparison of laboratory indicators and clinical adverse reactions in each group.

The detailed statistical analysis methods are detailed in the statistical analysis plan.

### 2. ACCESS TO ANALYSIS RESULTS

Prior to the DMC meeting, DMC members should receive and review the test study materials and study data in advance. In open meetings, study materials and data should be blind; In close meeting, study materials and study data are non-blind, that is, study materials and study data use a code that distinguishes treatment groups. Adequate confidentiality and security measures should be taken to ensure that there is no disclosure to parties outside the closed meeting.

Only DMC members can obtain to the study results before the sponsor makes them public. Prior to the completion of the study, any DMC member who discloses data will be immediately removed from the DMC membership.

No discussion of the DMC agreement or DMC proposals, whether written or oral, is allowed outside the DMC. The results of the study must be kept strictly confidential and must not be disclosed to anyone other than a member of the DMC until the recommendation to publish the results has been accepted and taken effect.

DMC 铭康 TNK III 期

V1.0 2021-02-04

After the DMC meeting, collect and distribute all paper DMC statistical analysis reports to DMC members, keep two copies and the remaining report were destroyed. One copy is kept by the DMC statistician and the other is kept by the DMC chairman in the secure file.

## VII. EXCHANGE AND COMMUNICATION

### 1. DATA DELIVERY

#### (1) Kick-off meeting materials

Documentation related to the meeting (including protocol, investigator's brochure and analysis plan) should be delivered to DMC members by express or E-mail 7 working days before the start of the meeting, so that DMC members can have enough time for review. Materials will be transmitted with electronic encryption protection.

#### (2) Planned review/monitoring of meeting materials

7 working days before the meeting, the data department will periodically clean up, lock the accumulated data and send it to independent statisticians in SAS format by mail, so that independent statisticians have enough time for statistical analysis. Related analysis reports include but are not limited to.

The following: serious adverse events, adverse events, list of violations or deviations from the protocol, research progress reports, list of dropped subjects, and/or statistical analysis reports (divided into blind open meeting reports and unblinded closed meeting reports).

The blind report is sent to DMC members 7 working days before each meeting or when the DMC requests it, and the non-blind report is printed by an independent statistician and bring to the meeting site.

### 2. MINUTES OF DMC MEETINGS

A recording of the meeting may be made for the objectives of writing the minutes. Once the chairman approves the minutes, the recording should be destroyed. The sponsor or its designee should keep minutes of the open meeting. This part of the minutes should only record the proceedings of the open meeting. The draft of the meeting minutes will be sent to the participants for review and comments and forwarded to the DMC chairman and sponsor for

DMC 铭康TNK III 期

V1.0 2021-02-04

review (within 7 working days) after the meeting.

Close meeting minutes record the proceedings of the closed meeting. The DMC administrative assistant is responsible for records. If discussion of non-blind data is involved in a close meeting, the meeting minutes, including non-blind information, will be marked "confidential" and send only to DMC members and statisticians. At the end of the study, the DMC administrative assistant sends a complete set of minutes of the open and closed meetings to the sponsor.

### 3. DMC PROPOSAL

DMC proposal should be made in a written document signed by all DMC members, within 5 working days after the end of the meeting, a clear message to sponsors of decision management, and then by sponsors decision-making management to default (signature/stamp written document) to sponsors project team, not by the DMC directly to the project team. The content recommended by the DMC should strictly adhere to the preset framework and follow a process decided jointly with the sponsor to minimize the DMC's contact with the project team and to eliminate potential bias and impact on trial execution.

The DMC should present its suggestions to the sponsor in a very clear and accurate manner. The DMC proposal, which mainly includes safety and study execution considerations, will be conducted in accordance with the guidelines set out in this charter. The proposal may include a small amount of clear and unambiguous data for the sponsor to make a reasonable decision on the proposal. The DMC proposal must include the date of the meeting, the location of the meeting, the status of the analytical data, the DMC committee suggestions, and the signature and date of the DMC members. Suggestions include but are not limited to:

- Continue the trial without revision of the protocol (carry out according to the established study protocol);
- Continue the trial after the revision of the protocol (e.g. adjust the sample size, dose, etc.);
- Suspend enrollment until uncertainty issues (such as potentially serious safety issues) are resolved;
- Terminate the trial (e.g. based on observed effectiveness, ineffectiveness, or serious safety issues).

DMC 铭康TNK III 期

V1.0 2021-02-04

The ultimate responsibility for the clinical trial rests with the sponsor, so the sponsor may choose to accept or reject the DMC recommendation, but if the sponsor rejects the DMC suggestions, especially regarding the termination of the study, it should reply to the DMC in writing and inform the ERB and the regulatory authorities.

### **VIII. ARCHIVING OF DOCUMENTS AND MATERIALS**

Need to archive the following documents (including but not limited to) : DMC charter , members list, statement of conflict of interest, confidentiality agreement, all accounting records (including reward and compensation for DMC members), the meeting agenda, the meeting minutes, DMC received a copy of all the documents (including the sponsor of the report, a copy of the DMC submitted to the sponsor's advice, the DMC copies of all official letters), all files are stored in a locked filing cabinet, Administrative assistant by the DMC limited access security area.

### **IX. AMENDMENT OF DMC CHARTER**

The starting meeting will discuss and modify the draft of DMC constitution submitted by the sponsor in advance, and the revised constitution will take effect after the approval of the chairman and the sponsor. If necessary, the effective DMC charter can also be amended. After the change, the charter will update the version, re-approve, and record the content, reason and date of the version update. In order to clearly display all deleted and modified text, it is recommended to keep the revised version with every trace of change.



DMC 铭康 TNK III 期

V1.0 2021-02-04