

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.**

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## DMC charter signing page

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**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:

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**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:

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Signed by members of the Clinical Trial Data Safety  
Monitoring Committee

DMC member:

Signature:

Date:

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Monitoring Committee

DMC member:

Signature:

Date:

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**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:

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

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## 1. STUDY OBJETIVES

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**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) .

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- ⑥ Deaths from any cause within 90 days.

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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

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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

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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



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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.

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- (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.

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- (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

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## 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

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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

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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.

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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

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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).



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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

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*Confidential*

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