

# Is tenecteplase ready to replace alteplase to treat acute ischaemic stroke? The knowns and unknowns

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Tenecteplase (TNKase, TNK-tPA or TNK) is a thrombolytic agent derived from the tissue plasminogen activator (tPA). It is a 527-amino acid glycoprotein developed by replacing three amino acids at the T, N and K positions of the glycoprotein structure of tPA under genetic recombinant technology. After replacing threonine 103 with asparagine, asparagine 117 with glutamine and a tetra-alanine at amino acids 296–299, TNK is about eightfold more potent in dissolving clot, 80-fold higher resistance to plasminogen activator inhibitor-1 and 14-fold enhanced relative fibrin specificity, and with a longer half-life (20 min).<sup>1</sup> Hence, TNK is administered as a single intravenous bolus.

TNK 0.5 mg/kg intravenous bolus is the choice in treating acute myocardial infarction (MI),<sup>2</sup> and was approved by the United States Food and Drug Administration in 2000. In comparison, the optimal dosages of TNK used alone or as a part of the bridging therapy remain to be further defined. For Caucasians patients with acute ischaemic stroke (AIS), TNK was tested at doses of 0.1, 0.25, 0.4 or 0.5 mg/kg.<sup>3–7</sup>

In the current issue of the journal, Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events (TRACE) trial tested three different doses of TNK versus standard dose of tPA in Chinese patients with AIS within 3 hours of onset.<sup>8</sup> The trial is a dose selection phase II trial with a multicentre, prospective, randomised, open label, blinded-endpoint (PROBE) controlled design recruiting AIS patients with severity of National Institutes of Health Stroke Scale (NIHSS) 4–25. No difference in safety was revealed between different dose groups compared with tPA in terms of symptomatic intracerebral haemorrhage (sICH) events (5.0% in 0.1 mg/kg, 0.0% in 0.25 mg/kg, 3.3% in 0.32 mg/kg TNK and 1.7% in 0.9 mg/kg tPA;  $p=0.52$ ). Also, no significant difference in any efficacy outcomes was observed. The study may be statistically underpowered due to a small sample size.

The Norwegian Tenecteplase Stroke Trial (NOR-TEST) showed a similar efficacy and safety profile between the TNK (0.4 mg/kg) and tPA in patients with mild AIS within 4.5 hours of onset.<sup>9</sup> In its subgroup analysis, the distribution of favourable outcome and sICH were similar between treatment groups in patients with moderate and severe stroke. However, all-cause mortality in patients with severe strokes at 90 days was increased in the TNK group (26.3% vs 9.1%;  $p=0.045$ ).<sup>10</sup>

Imaging assessment has been used as a surrogate marker to compare the efficacy of TNK to that of tPA. The Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) trial compared TNK 0.25 mg/kg to tPA 0.9 mg/kg in patients with AIS treated within 4.5 hours of onset. ATTEST failed to show a significant improvement of salvaged penumbra in the TNK group.<sup>11</sup> The Australian-TNK trial required a large vessel occlusion on baseline CT angiography and substantial mismatch on baseline CT perfusion imaging to select patient for either TNK 0.1 or 0.25 mg/kg versus standard dose of tPA within 3 hours of onset.<sup>5</sup> The trial showed better early neurological improvement, reperfusion and higher rates of favourable 90-day outcome in patients treated with 0.25 mg/kg of TNK. The pooled analysis of ATTEST and Australian-TNK trials showed that TNK-treated patients with a TICI (Treatment in Cerebral Ischemia Score) 0/1 occlusion had higher rate of complete recanalisation at 24 hours (71% vs 43%,  $p<0.001$ ) and had better early clinical improvement and favourable 90-day outcomes.<sup>12</sup> Further analysis stressed the importance of target perfusion mismatch.<sup>13</sup> The EXTEND-IA TNK study showed that TNK (0.25 mg/kg) before thrombectomy was associated with a higher rate of reperfusion and better functional outcome than the standard dose of tPA in AIS patients with an large vessel occlusion (LVO), if treated within 4.5 hours of onset.<sup>14</sup> EXTEND-IA TNK Part 2 showed that TNK doses of either 0.40 or 0.25 mg/kg had no

**Table 1** Ongoing and planned clinical trials examining the efficacy and safety of TNK

| Trial Type                | Trial Name                                                                                                 | Objectives                                                                                                                                     | Study design                                                                                                                                                             | Primary outcome        | Key safety outcome                                                               | Key eligibility criteria                                                                                                                                                                                                                                                      | Registration number |
|---------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Within 4.5 hours of onset | AcT (Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke)                            | To test the real-world non-inferiority of TNK efficacy compared with tPA in patients with AIS eligible for IV thrombolysis                     | TNK 0.25 mg/kg vs tPA 0.9 mg/kg non-inferiority<br>Pragmatic registry-based phase III randomisation: Yes<br>Open label: Yes<br>Blinded outcome assessment: Yes<br>N=1600 | mRS at day 90–120      | Mortality and sICH                                                               | Patients with AIS eligible for IV tPA or bridging therapy                                                                                                                                                                                                                     | NCT03889249         |
|                           | ATTEST 2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis)                                 | To test the superiority of TNK efficacy compared with tPA in patients with AIS eligible for IV thrombolysis                                    | TNK 0.25 mg/kg vs tPA 0.9 mg/kg Phase III randomisation: Yes<br>Open label: Yes<br>Blinded outcome assessment: Yes<br>N=1870                                             | mRS at day 90          | Intracranial and extracranial haemorrhage, mortality, neurological deterioration | ≥18 years old<br>Thrombolysis initiated within 4.5 hours after onset<br>Eligible for IV thrombolysis<br>Premorbid mRS 0–1                                                                                                                                                     | NCT02814409         |
|                           | NOR TEST 2 (The Norwegian Tenecteplase Stroke Trial 2)                                                     | To compare efficacy and safety of TNK vs tPA 0.9 mg/kg within 4.5 hours after onset, including wake-up stroke and before EVT                   | TNK 0.4 mg/kg vs tPA 0.9 mg/kg non-inferiority<br>Phase III randomisation: Yes<br>Open label: Yes<br>Blinded outcome assessment: Yes<br>N=1342                           | % of mRS 0–1 at day 90 | Cerebral haemorrhages on CT/MRI within 24–48 hours and mortality                 | ≥18 years old<br>Thrombolysis initiated within 4.5 hours after onset<br>NIHSS >5<br>Premorbid mRS 0–2                                                                                                                                                                         | NCT03854500         |
| Large vessel occlusion    | BRETIS-TNK (Boosting REcanalization of Thrombectomy for Ischemic Stroke by Intra-arterial TNK)             | To explore whether a combination of IA TNK and EVT can increase recanalisation rate after the first attempt of device pass                     | IA TNK 4 mg bolus followed by infiltration (0.4 mg/min) for 30 min<br>Single arm phase: Not applicable<br>N=30                                                           | % of TICl 2b-3         | sICH                                                                             | ≥18 years old<br>LVO anterior circulation stroke eligible for EVT<br>TOAST: LAA                                                                                                                                                                                               | NCT04202458         |
|                           | TASTE (Tenecteplase vs Alteplase for Stroke Thrombolysis Evaluation)                                       | To test TNK's efficacy in patients with demonstrated LVO and target penumbral pattern as opposed to tPA within 4.5 hours                       | TNK 0.25 mg/kg vs tPA 0.9 mg/kg non-inferiority<br>Phase III randomisation: Yes<br>Open label: Yes<br>Blinded outcome assessment: Yes<br>N=1024                          | mRS 0–1 at day 90      | sICH and all cause death                                                         | ≥18 years old<br>Thrombolysis initiated within 4.5 hours after onset<br>Eligible for IV thrombolysis<br>Premorbid mRS 0–1<br>Imaging selection criteria:<br>Penumbra volume >15 mL;<br>mismatch ratio >1.8;<br>ischaemic core <70 mL;<br>severely hypoperfused volume <100 mL | ACTRN12613000243718 |
|                           | TEMPO 2 (TNK–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion) | To test TNK's efficacy compared with standard care, in patients of TIA or minor stroke with demonstrated LVO or near occlusion within 12 hours | TNK 0.25 mg/kg vs antiplatelets<br>Phase III randomisation: Yes<br>Open label: Yes<br>Blinded outcome assessment: Yes<br>N=1274                                          | mRS at day 90          | Major bleeding                                                                   | ≥18 years old<br>Treatment can be initiated within 12 hours after onset, and within 90 min of the start of CT/MRI<br>TIA or minor stroke with NIHSS ≤5<br>Acute LVO or near occlusion (TICI 0 or 1)<br>Premorbid mRS 0–2                                                      | NCT02398656         |

Continued

**Table 1** Continued

| Trial Type                          | Trial Name                                                                                                                | Objectives                                                                                                            | Study design                                                                                                                                     | Primary outcome                                                                                                                                                    | Key safety outcome                            | Key eligibility criteria                                                                                                                                                                                                                                                        | Registration number |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Late time window or wake-up strokes | CHABLIS-T (Chinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase)                                | Optimal dosage determination of TNK in AIS patients in extended time window.                                          | TNK 0.25 mg/kg vs TNK 0.32 mg/kg Phase II randomisation: Yes Open-label: Yes Blinded outcome assessment: Yes N=86                                | For patients w/o EVT:>50% reperfusion at 4–6 hours and w/o sICH at 24–48 hours For patients with EVT: mTICI score $\geq 2b$ before EVT and w/o sICH at 24–48 hours | ICH, systemic bleeding and mRS 5–6            | $\geq 18$ years old 4.5–24 hours after onset Anterior circulation AIS Premorbid mRS 0–2 Clinically significant neurological deficits Imaging selection criteria: Proven LVO or severe stenosis; mismatch ratio $>1.2$ ; ischaemic core $<70$ mL; absolute difference $>10$ mL   | NCT04086147         |
|                                     | ETERNAL-LVO (Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion) | To evaluate the efficacy and safety of TNK in extended time window                                                    | TNK 0.25 mg/kg vs standard care (may include eligible IV tPA) Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=740 | mRS 0–1 or return to baseline mRS (if premorbid mRS=2) at day 90                                                                                                   | ICH, all cause death, infarct growth, mRS 5–6 | $\geq 18$ years Up to 24 hours after onset or last known well Anterior circulation AIS Premorbid mRS 0–2 Imaging selection criteria: Proven LVO or extracranial ICA stenosis; mismatch ratio $>1.8$ ; ischaemic core $<70$ mL; absolute difference $>20$ mL                     | NCT04454788         |
|                                     | ROSE-TNK (MRI-guided thrombolysis for Stroke beyond Time Window by TNK)                                                   | To examine the feasibility and outcome of TNK in 4.5–24 hours after stroke guided by a mismatch between DWI and FLAIR | TNK 0.25 mg/kg vs standard care Phase IV randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=80                                 | mRS 0–1 at day 90                                                                                                                                                  | ICH, any bleeding events and death            | 18–80 years old 4.5–24 hours after onset NIHSS 6–25, or NIHSS $\leq 5$ with culprit vessel occlusion or severe stenosis Premorbid mRS 0–1 Imaging selection criteria: DWI infarct $<1/3$ of MCA or $1/2$ of ACA or $1/2$ of PCA territory; infarct $<70$ mL; DWI/FLAIR mismatch | NCT04752631         |
|                                     | TIMELESS (Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase)       | To evaluate the efficacy and safety of TNK in extended time window                                                    | TNK 0.25 mg/kg vs placebo Phase III randomisation: Yes Blinded treatment: Yes Blinded outcome assessment: Yes N=456                              | mRS at day 90                                                                                                                                                      | ICH, adverse events, mortality                | $\geq 18$ years old 4.5–24 hours after onset Anterior circulation AIS Premorbid mRS 0–2 NIHSS $\geq 5$ prior to randomisation Imaging selection criteria: Proven LVO; mismatch ratio $\geq 1.8$ ; Ischaemic core $<70$ mL; absolute difference $\geq 15$ mL                     | NCT03785678         |

Continued

Table 1 Continued

| Trial Type | Trial Name                                                           | Objectives                                                        | Study design                                                                                                                                            | Primary outcome | Key safety outcome      | Key eligibility criteria                                                                                                                     | Registration number |
|------------|----------------------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
|            | TWIST (Tenecteplase in Wake-Up Ischaemic Stroke Trial) <sup>18</sup> | To test TNK's efficacy in stroke patients <4.5 hours of awakening | TNK 0.25 mg/kg+standard care vs no TNK +standard care<br>Phase III<br>randomisation: Yes<br>Open label: Yes<br>Blinded outcome assessment: Yes<br>N=600 | mRS at day 90   | All-cause death and ICH | ≥18 years old<br>Wake-up stroke<br>With limb weakness with NIHSS of 3–24, or dysphasia<br>Treatment can be initiated <4.5 hours of awakening | NCT03181360         |

ACA, anterior cerebral artery; AIS, acute ischaemic stroke; DWI, diffusion-weighted imaging; EVT, endovascular therapy; FLAIR, fluid attenuation inversion recovery; IA, intra-arterial; ICA, internal carotid artery; ICH, intracerebral haemorrhage; IV, intravenous; LAA, large artery atherosclerosis; LVO, large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; mTICI score, Modified Treatment in Cerebral Ischemia Score; sICH, symptomatic intracerebral haemorrhage; TNK, tenecteplase; TOAST, Trial of Org 10172 in Acute Stroke Treatment; tPA, tissue plasminogen activator; tPA, tissue plasminogen activator;

difference in improving cerebral reperfusion prior to endovascular thrombectomy. However, sICH occurred in seven patients (4.7%) in the 0.40 mg/kg group compared with two patients (1.3%) in the 0.25 mg/kg group (risk ratio 3.50, 95% CI 0.74 to 16.62;  $p=0.12$ ).<sup>6</sup>

With limited evidence, the 2019 AIS guideline of the American Heart/Stroke Association recommended TNK 0.4 mg/kg as an alternative to tPA in selected patients with AIS of minor neurological impairments and no major intracranial occlusion, while TNK 0.25 mg/kg for LVO patients prior to thrombectomy (both with level of evidence (LOE): B-R, and class of recommendation (COR): IIB).<sup>15</sup>

Current limited evidence supports no superiority of either dose over the other (0.25 mg/kg vs 0.4 mg/kg). Yet, dosage of 0.25 mg/kg is most frequently used in ongoing trials of TNK in AIS (table 1), with a support of its efficacy based on a recent network meta-analysis.<sup>16</sup> In addition, TNK's efficacy when used in patient with LVO was only seen with imaging-based endpoints, while its safety is comparable to tPA. Therefore, its solid effects in treating AIS remain to be studied. TNK is likely to have its role to treat AIS, but more data are needed for it to completely replace tPA.

A series of ongoing phase III trials will further address the efficacy and safety of TNK either within early or late time windows, with or without LVO (table 1). Particularly in China, the ongoing TRACE II trial is testing the efficacy of TNK 0.25 mg/kg (single bolus, max 25 mg) as opposed to standard dose of tPA.<sup>17</sup> TRACE III will study TNK in AIS due to LVO with perfusion mismatch up to 24 hours of symptom onset.

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#### REFERENCES

- Keyt BA, Paoni NF, Refino CJ, *et al*. A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci U S A* 1994;91:3670–4.
- , Van De Werf F, Adgey J, *et al*. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the assent-2 double-blind randomised trial. *Lancet* 1999;354:716–22.
- Haley EC, Lyden PD, Johnston KC, *et al*. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. *Stroke* 2005;36:607–12.
- Thompson JLP, Thompson JLP, Grotta JC, *et al*. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke* 2010;41:707–11.
- 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.
- 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;323:1257–1265.
- Coutts SB, Dubuc V, Mandzia J, *et al*. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke* 2015;46:769–74.
- Li S, Pan Y, Wang Z, *et al*. Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (trace): a multicentre, randomised, open label, blinded-endpoint (probe) controlled phase II study. *Stroke Vasc Neurol* 2021;svn-2021-000978.
- 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.
- Kvistad CE, Novotny V, Kurz MW, *et al*. Safety and outcomes of tenecteplase in moderate and severe ischemic stroke. *Stroke* 2019;50:1279–81.
- 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.
- Bivard A, Huang X, Levi CR, *et al*. Tenecteplase in ischemic stroke offers improved recanalization: analysis of 2 trials. *Neurology* 2017;89:62–7.

- 13 Bivard A, Huang X, McElduff P, *et al.* Impact of computed tomography perfusion imaging on the response to tenecteplase in ischemic stroke: analysis of 2 randomized controlled trials. *Circulation* 2017;135:440–8.
- 14 Campbell BCV, Mitchell PJ, Churilov L, *et al.* Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573–82.
- 15 Powers WJ, Rabinstein AA, Ackerson T, *et al.* Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 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.
- 16 Kheiri B, Osman M, Abdalla A, *et al.* Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. *J Thromb Thrombolysis* 2018;46:440–50.
- 17 Li S, Campbell BCV, Schwamm LH, *et al.* Tenecteplase reperfusion therapy in acute ischaemic cerebrovascular events-II (trace II): rationale and design. *Stroke Vasc Neurol* 2021. doi:10.1136/svn-2021-001074. [Epub ahead of print: 26 Aug 2021].
- 18 Roaldsen MB, Lindekleiv H, Eltoft A, *et al.* Tenecteplase in wake-up ischemic stroke trial: protocol for a randomized-controlled trial. *Int J Stroke* 2021;1747493020984073. doi:10.1177/1747493020984073